DÉVELOPPEMENT DE RÉACTIONS D'ANALOGUES D'ÉNOLS PROMUES PAR DES IODANES

par

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SOMMAIRE

Le projet de maitrise consistait en l'évaluation de la réactivité de nouveaux substrats (haloalcènes), encouragé par les résultats précédents au laboratoire de Claude Y. Legault, réalisés par Benoit Basdevant. La réaction a été prouvée, optimisée, puis appliquée.

D'abord, une introduction à l'iode hypervalent sera présentée.

Le premier chapitre consiste en la présentation d'un premier article. Il s'agit d'une revue de la littérature qui relate de la réactivité d'analogues d'énol et d'ynol vis-à-vis de réactifs d'iode hypervalent. Il fait état des travaux poursuivis dans le laboratoire de Claude Y. Legault et met en contexte les recherches effectuées lors du projet de maitrise.

Le deuxième chapitre présente les résultats de ces recherches, soit la publication de la transposition oxydante d'haloalcènes en α-halocétones par un réactif d'iode hypervalent et des premiers pas vers une réaction stéréosélective.

Iode hypervalent, fonctionalisation cétone, halogénation, énol, ynol, anologue d'énol, α-halo cétone.

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Alk	alkyle
Ar	aryle
Ar*	aryle chiral
Ac	acétyle
Bn	benzyle
Bz	benzoyle
Boc	butoxycarbonyle
Cbz	carboxybenzyle
DCE	dichloroéthane
DMF	diméthylformamide
CTAB	bromure de cétyl triméthylammonium
ee	excès énantiomérique
EWG	groupement électroattracteur
HOMO	orbitale moléculaire pleine la plus haute en énergie
HTIB	hydroxy(tosyloxy)-iodo]benzene
LUMO	orbitale moléculaire vide la plus basse en énergie
m-CPBA	acide *meta*-chloroperbenzoïque
Ms	mésyle
NIS	*N*-iodosuccinimide
Ns	nosyle
Nu	nucléophile
PG	groupement protecteur
Ph	phényle
PIDA	diacétoxyiodobenzène
PIFA	bistrifluorooroiodobenzène
PMB	*para*-méthoxybenzyle
R_F	perfluoroalkyle
SET	transfert mono-électronique
S_N2	substitution nucléophile de deuxième ordre
TBDMS	*tert*-butyldiméthylsilyle

TEMPO	(2,2,6,6-Tétraméthylpipéridin-1-yl)oxyle
Tf	triflate
TFA	acide trifluoroacétique
TMS	triméthylsilyle
Tol	tolyle
Ts	tosyle

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INTRODUCTION

I.1 L'iode : histoire du 53^{ième} élément[1,1]

L'iode est l'élément commun le plus gros de la famille des halogènes. De tous ses isotopes, de ^{108}I à ^{144}I, un seul est stable et n'entreprend pas une désintégration nucléaire spontanée. Il s'agit de ^{127}I. On le retrouve surtout sous forme d'iode moléculaire : I_2. Sa découverte en 1811 est attribuée à un chimiste français : Bernard Courtois. Il a rapporté la condensation d'un gaz violet en un solide d'apparence métallique lors du déroulement d'un processus pour obtenir des sels de potassium depuis des cendres d'algues.

Au début des années 1800, la France était en guerre et en pénurie de cendres de bois, dont les sels de potassium étaient utilisés dans le processus de production de nitrate de potassium. Comme ce dernier était largement utilisé dans la confection de poudre à fusil, une forte hausse de la demande pour des produits de remplacement a encouragé de nombreux Français, tel que le chimiste Bernard Courtois, à exercer le métier de salpêtrier. Ces derniers se sont tournés vers les cendres peu coûteuses d'algues provenant de Bretagne et de Normandie pour produire du carbonate de potassium. En entreprenant la lixiviation des cendres avec de l'eau, du K_2CO_3 contaminé par divers sels et impuretés était obtenu. L'étape suivante consistait en l'ajout d'acide sulfurique à l'extrait pour éliminer les impuretés contenant du soufre. Il en résultait l'acquisition de carbonate de potassium bon marché, qui servirait à entretenir la machine de guerre. L'observation d'une inhabituelle corrosion du cuivre pendant le processus aurait encouragé le salpêtrier Bernard Courtois à en déterminer les causes. Lors de ses expériences, l'ajout d'une quantité un peu plus importante d'acide aurait causé un exotherme important, suivi d'un dégagement de vapeurs pourpres formant des cristaux lors d'un contact avec des surfaces froides, dont la couleur et le lustre étaient comparés à ceux du graphite. La découverte de cette nouvelle substance l'aura rendu célèbre dans les années qui allaient suivre. Avant celles-ci, il a continué de gérer sa profitable entreprise tout en menant des expériences sur sa découverte dans son laboratoire. Après qu'il ait délégué ses recherches à des collègues, ces derniers ont tardé à faire part de la trouvaille à l'Institut de France (l'Académie des sciences de l'époque). Entretemps, il a été démontré que la substance était indécomposable et analogue au chlore moléculaire. Comme ce dernier, un acide était formé lors de son

[1] Swain, P. A. *Bull. Hist. Chem.* **2005**, *30*, 103-111.

hydrogénation. Ces expériences ont confirmé qu'il s'agissait d'un nouvel élément. En 1813, la découverte a finalement fait l'objet d'une publication par le professeur de chimie Nicholas Clément. Il a honoré ses collègues en mettant Bernard Courtois comme auteur et en donnant le nom d'iode au nouvel élément, du mot grec ιώδες (*iodes*) signifiant violet, tel que suggéré par Joseph Louis Gay-Lussac en 1811, un chimiste déterminant du comité de recherche. Plus tard, une explication pour la génération d'iode à partir des cendres d'algues et d'acide sulfurique a été rationalisée. Il s'agit d'une réaction d'oxydoréduction entre de l'iodure de sodium et l'acide sulfurique en produisant de l'iode, du sulfate de sodium et de l'eau (équation 1). La corrosion, quant à elle, se produit par oxydation du cuivre en iodure de cuivre(II) par l'iode en présence d'acide et de chaleur (équation 2). Le sel de cuivre(II) instable se décompose en iodure de cuivre(I) et dégageant de l'iode (équation 3).

$$8\ NaI + 5\ H_2SO_4 \rightarrow 4\ I_2 + 4\ Na_2SO_4 + 4\ H_2O$$

Équation 1.

$$Cu + I_2 + HI \xrightarrow{\Delta} CuI_2 + HI$$

Équation 2.

$$2\ CuI_2 \rightarrow 2\ CuI + I_2$$

Équation 3.

Il n'a fallu que quelques années pour découvrir que l'iode peut former une multitudes de composés organiques et inorganiques dans lesquels son état d'oxydation peut être de -1, +1, +3, +5 ou de +7. Les premiers composés d'iode hypervalent, d'états d'oxydation +3, +5 et +7, sont apparus rapidement dans la littérature par oxydation, en présence d'un excès de chlore, du chlorure scientifique. En 1814, Joseph Louis Gay-Lussac a publié la synthèse du premier composé d'iode hypervalent : le chlorure d'iode(III).[2] Il est obtenu d'iode(I) ou de l'iode chaud.[3] L'étude des propriétés structurales et électroniques des composés de ces exotiques composés d'iode a démontré qu'ils possèdent une géométrie particulière et une couche de valence supérieure à 8 électrons, soit une hypervalence. La rationalisation de ces constats n'était pas cohérente avec la théorie de Lewis-Langmuir[4,5]. Bien que cette dernière ait été consistante dans l'explication et la prédiction des structures électroniques et la géométrie de la vaste majorité des composés organiques, aucune nouvelle théorie n'aura été avancée avant le 20^{ième} siècle pour expliquer ces exceptions à la règle. Toutefois, l'exploration de ce type de composés a permis à la communauté

scientifique de développer de nouvelles réactions utiles, en plus d'apporter une nouvelle perspicacité vis-à-vis l'hypervalence.

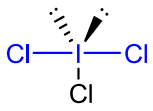
I.2 Iode hypervalent[6]

Conscient des répercussions scientifiques qu'apporteraient une meilleure compréhension du phénomène d'hypervalence[7], le chimiste Jeremy L. Musher s'est entaché de changer le discours largement répandu dans la communauté selon lequel les composés hypervalents ne seraient que des exceptions à la théorie Lewis-Langmuir. Il y est parvenu en publiant un article en 1969, dans lequel il propose un modèle pour l'hypervalence à partir de la théorie des orbitales moléculaires.[8]

I.2.1. Distinction et définition du nouveau modèle

On donne le qualificatif d'hypervalent à tous les composés et les ions comportant des éléments des groupes V à VIII lorsque leur valence chimique excède celle permise par la théorie de Lewis-Langmuir. Selon cette définition, XF_2 est une molécule hypervalente comme l'atome de Xénon est divalent et dépasse par deux sa valence chimique traditionnellement permise de zéro. Il est suggéré que la somme des paires d'électrons libres du xénon et de celles impliquées dans ses liaisons ne correspond pas à la valence électronique de l'atome en question, contrairement à ce qu'on obtiendrait d'un décompte électronique traditionnel. En d'autres mots, les atomes hypervalents ne respectent pas la règle de l'octet lorsqu'on fait le décompte électronique en utilisant la formule de Lewis.

À l'instar du décompte électronique, le modèle classique ne parvient pas à expliquer la géométrie des composés hypervalent, telle que celle du ICl_3.



I-1

Figure 1. Structure du ICl_3 (lien hypervalent en bleu)

L'élucidation de sa structure, prenant la forme de bipyramide à base triangulaire où deux chlorures occupent les positions axiales et où le dernier chlorure et les deux paires d'électrons libres de l'iode occupent les positions équatoriales, a révélé deux types de liaisons I-Cl de différentes longueurs (figure 1). Il s'agit d'une caractéristique unique aux composés hypervalents tels le PF_5, le IF_7 et le SF_4. Si ce n'était des évidences expérimentales, on aurait prédit des liens de longueurs identiques pour des ligands identiques.

Musher a soutenu que la présence de plus de huit électrons de valence, en suivant la formule de Lewis, et de longueurs de liens différentes pour des ligands identiques suggèrent que ces molécules comportent des liaisons covalentes ainsi qu'un second type de liaison de force moindre. Cette proposition serait cohérente avec le modèle classique où le décompte électronique ne s'applique qu'aux liaisons covalentes. À partir de la théorie des orbitales moléculaires, il a montré qu'on peut ne pas contrevenir à la règle de l'octet et expliquer les différentes longueurs de liaisons en avançant le modèle du lien hypervalent.

I.3 Modèle de la liaison hypervalente à trois centres et quatre électrons (3c-4e)

Le lien hypervalent comporte trois centres linéaires et quatre électrons. Par exemple, on peut appliquer ce nouveau modèle au ICl_3 en exemple, la liaison Cl_{axial}-I-Cl_{axial} du est linéaire, contient quatre électrons et est nommée : liaison hypervalente. Elle se distingue de la liaison σ I-$Cl_{équatorial}$, qui est plus courte et de caractère covalent. Cette idée découle de la théorie des orbitales molécules, selon laquelle une orbitale moléculaire nait d'une combinaison linéaire des orbitales atomiques impliquées dans les liaisons. Musher applique le concept de lien 3c-4e, introduit deux décennies plus tôt par George C. Pimentel[9] et Robert E. Rundle[10], pour décrire la liaison hypervalente par trois nouvelles orbitales provenant de la combinaison linéaire des trois atomes impliqués. Tel qu'illustré à la figure 2, la liaison hypervalente du chlorure d'iode(III) est décrite par la combinaison linéaire de deux orbitales 3p et une orbitales 5p contenant un total de quatre électrons.

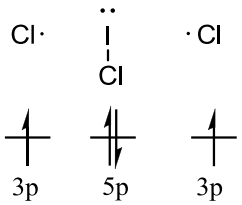


Figure 2. Orbitales atomiques impliquées dans la liaison hypervalente du ICl_3

De cette combinaison naissent trois nouvelles orbitales décrivant la liaison hypervalente (figure 3). Ce modèle permet donc de se faire une idée plus claire de la répartition de la densité électronique à l'intérieur de chacune des trois nouvelles orbitales

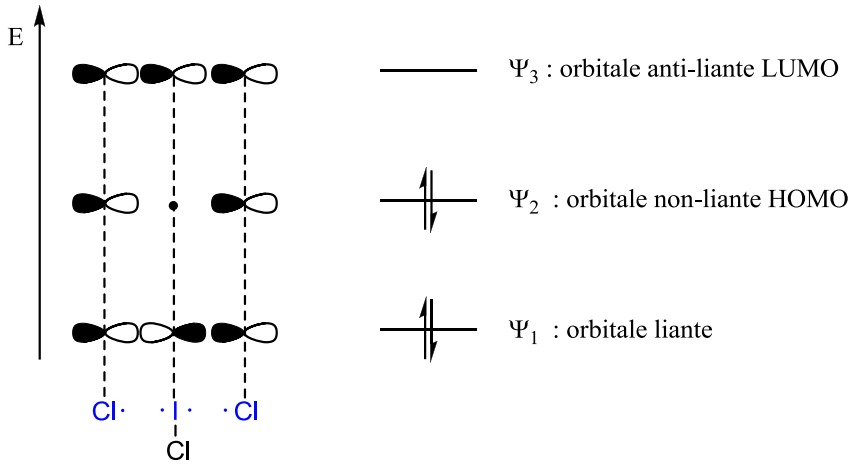


Figure 3. Orbitales à 3c-4e décrivant la liaison hypervalente du ICl_3

L'orbitale Ψ_1 ne comporte aucun point nodal, car tous les lobes sont en phase. Elle constitue l'orbitale liante de plus basse énergie où la répartition des deux électrons est semblable entre les trois atomes, ce qui lui confère un caractère covalent. L'orbitale Ψ_2 comporte un point nodal centré sur l'iode et deux lobes sur les ligands. Il s'agit d'une orbitale non-liante qui contient deux électrons faisant de celle-ci la HOMO de la liaison hypervalente. La densité électronique serait nulle sur l'iode et grande sur les ligands. Elle est donc très polarisée et s'apparente à une liaison ionique.

Grâce à ce modèle intuitif, on peut mieux expliquer la différence de longueurs entre les liens I-Cl_{axiaux} et σ I-$Cl_{équatorial}$. En effet, elle a un ordre de liaison unitaire, et par le fait même, chaque lien I-Cl_{axial} a un ordre de liaison de 0.5, soit la moitié de celui du lien covalent σ I-$Cl_{équatorial}$. La différence d'ordres de

liaison et donc de longueurs de liens est cohérente avec les évidences expérimentales. La figure 3 nous permet de visualiser et de rationaliser la nature de la liaison hypervalente. La Ψ_1 confère un certain caractère covalent à la liaison, alors que la Ψ_2 lui confère un certain caractère ionique. C'est certainement la raison pour laquelle ce sont les ligands les plus électronégatifs qui sont impliqués dans la liaison hypervalente, comme ils stabilisent mieux les électrons de la Ψ_2. En suivant cette logique, la force de la liaison hypervalente serait quelque part entre celle de la liaison ionique et covalente. Cette supposition corrèle tout à fait aux observations de longueurs de liens selon leur type. Les liens hypervalents sont plus courts que les liens ioniques et plus que ceux covalents[4].

I.4 Nomenclature

De façon générale, soit pour tous les composés hypervalents, deux nomenclatures populaires ont perduré. La prémière est celle de James C. Martin et Anthony J. Arduengo[11], mieux connue sous le nom de nomenclature N-X-L; elle nous informe sur la valence électronique classique (N) de l'atome central (X) et le nombre de ligands (L) auxquels il est lié (figure 4).

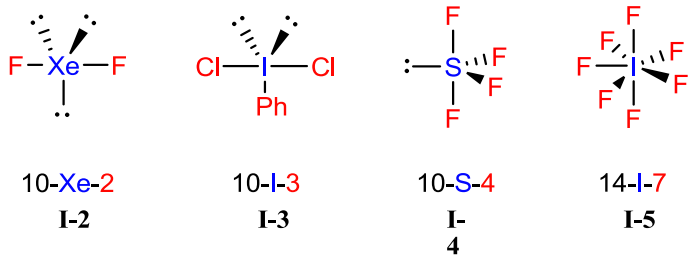


Figure 4. Nomenclature N-X-L du XeF_2, $PhICl_2$, SF_4 et IF_7

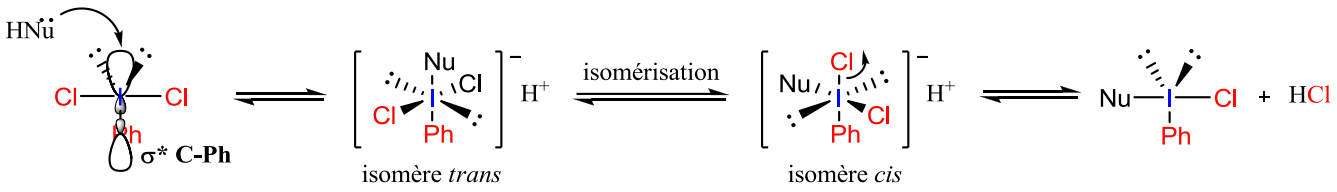
La deuxième manière populaire de nommer les composés hypervalents consiste en la norme UIPAC[12] : la notation lambda (λ). Elle permet de décrire l'état d'oxydation, la nature de l'espèce hypervalente et son nombre de ligands. On ajoute le préfixe λ^n- où n est le nombre de ligands sur l'élément hypervalent. Par exemple, le composé **I-2** est un λ^2-xénonane, **I-3** est un λ^3-iodane, **I-4** est un λ^4-sulphane et le composé **I-5** est un λ^7-iodane. Il s'agit de la nomenclature qui sera employé pour le restant du présent document.

I.5 Réactivité des λ^3-iodanes

Le projet de maîtrise consistait presqu'exclusivement au développement de nouvelles méthodologies et réactions promues des λ^3-iodanes de type $ArIX_2$. Il est donc avisé de discuter de leur réactivité qui rappelle celle de métaux de transitions, comme leurs propriétés permettent les réactions d'échange de ligands, de couplage réductif et d'élimination réductrice.

I.5.1. Les échanges de ligands chez les λ^3-iodanes de type $ArIX_2$

La polarisation importante du lien hypervalent ainsi que son niveau d'oxydation rendent l'atome d'iode fortement électrophile. À l'ajout d'un nucléophile, ce dernier peut attaquer l'iode là où se trouve l'orbitale anti-liante la moins encombrée, soit la σ* I-Ph du composé **I-3** pour former un anion tétravalent **I-6** de géométrie plan-carré. Il s'en suit un processus isomérisation à l'équilibre dans lequel le nucléophile Nü devient *cis* par rapport à l'aryle et *trans* pour le ligand électronégatif pour donner l'intermédiaire **I-7**. À cette étape, une neutralisation de l'anion par l'expulsion d'un ligand résulte en l'obtention d'un nouvel iodane **I-8** (schéma 1). Différents nucléophiles peuvent être échangés en contrôle thermodynamique, comme toutes les étapes sont à l'équilibre. Toutefois, si l'affinité du nucléophile à l'iodane est suffisamment importante, cette étape peut être irréversible.[4]



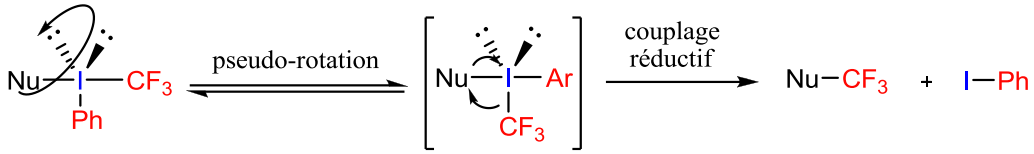
I-3 **I-6** **I-7** **I-8**

Schéma 1.

Cette voie mécanistique est qualifiée d'associative et serait probablement énergiquement favorisée par rapport à la voie dissociative. Cette dernière implique la formation difficile d'un intermédiaire iodonium hautement déficient en électrons avant l'association du nucléophile.

I.5.2. Couplages réductifs et éliminations réductrices[4]

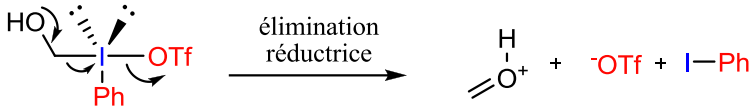
Étant donné la force importante du lien I-Ar et la remarquable nucléofugacité des iodoaryles, un couplage réductif formant un lien entre les deux ligands en éjectant de l'iodoaryle peut être observé et exploité en chimie organique. Conformément à l'exemple du schéma 2, l'iodane **I-9** peut entreprendre une pseudo-rotation à l'équilibre, menant à l'intermédiaire **I-10** qui a la géométrie *cis* nécessaire entre les partenaires pour permettre leur couplage en éjectant le composé d'iode réduit **I-11** et de l'iodobenzène.



I-9 **I-10** **I-11**

Schéma 2.

Lorsque les ligands ont une très grande différence d'électronégativité comme **I-12**, une élimination réductrice peut se produire spontanément pour former un sel et l'iodure réduit comme dans l'exemple fictif suivant (schéma 3).



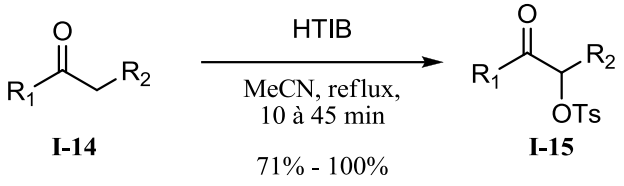
I-12 **I-13**

Schéma 3.

Ces réactions typiques ont été exploitées pour diverses réactions d'oxydations en chimie organique, notamment la réaction l'oxydation en α de carbonyles.

I.6 La réaction d' α-tosyloxylation de carbonyles

Un regain d'intérêt de la communauté scientifique pour la chimie des λ^3-iodanes a été attribué à Koser par sa publication sur l'α-tosyloxylation de carbonyles par l'hydroxy(tosyloxy)iodobenzène (HTIB) en 1982 (équation 4).[13]



R_1, R_2 = alkyle, aryle, hétéroaryle

Équation 4.

Cette réaction présente une complémentarité intéressante à la chimie du carbonyle où on le fonctionnalise en position α par la formation d'un anion énolate et de son attaque subséquente sur un électrophile. Cette inversion de polarité au carbone fonctionnalisé constitue une stratégie Umpolung. Les composés de types $ArIX_2$ comme le HTIB permettent l'introduction de nucléophiles par une double substitution électrophile (schéma 4). Le mécanisme actuellement proposé commence par l'échange d'un ligand sur le carbonyle **1-14** pour fournir un sel d'iodonium *O*-lié **I-16**. Il s'en suit d'une déprotonation pour mener au sel d'iodonium **I-17** dont l'anion effectue la réduction de l'iodobenzène par déplacement de type S_N2' en formant ainsi le carbonyle α-tosyloxylé **I-15**.

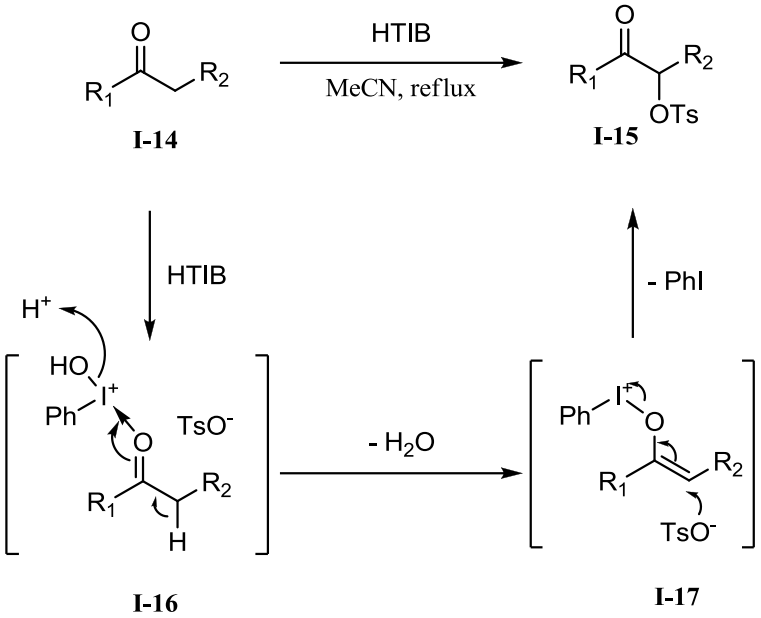


Schéma 4.

Comme le produit de la réaction est chiral et comporte un bon groupement partant, il permet une multitude de substitutions par des nucléophiles variés en passant par un mécanisme S_N2. Ce dernier garder l'information stéréochimique, donc plusieurs groupes de recherche se sont lancés dans le développement d'une variante stéréosélective pour obtenir des produits chiraux énantioenrichis. Malgré des efforts soutenus, l'utilisation de λ^3-iodanes chiraux n'a pas apporté d'excès énantiomériques très élevés.[14] Parmi ces chercheurs se trouvait Audrey-Anne Guibault, étudiante à la maîtrise en sein du groupe du P[r] Claude Y. Legault. Elle s'est investie dans le développement de nouveaux catalyseurs chiraux pour la réaction de Koser, mais qui n'ont malheureusement pas permis l'atteinte de hauts *ee*. Ses recherches se sont concentrées sur la synthèse d'un pré-catalyseur d'iode hypervalent chiral (figure 5) activé par du *m*-CPBA.

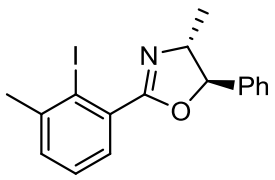


Figure 5. Pré-catalyseur d'iode hypervalent chiral

Il a été démontré que le groupement méthyle en position *ortho* était essentiel à la bonne activité du catalyseur. Le candidat optimal, ci-haut, a été utilisé pour tester la réaction stéréosélective d'α-tosyloxylation de cétones. À partir du substrat modèle, la propiophénone, avec les conditions stéréosélectives développées par Audrey-Anne, de l'alpha-tosyloxypropiophénone énantioenrichie a été obtenue avec des rendements allant de 73 à 93% et des excès énantiomériques allant de 29 à 36%. Une explication à ces bas *ee* a pu être avancée. On remarque avec le schéma 4 que l'intermédiaire **1-17** possède son carbone pro-chiral assez loin de l'iodane en replaçant Ph par Ar*. La chiralité de ce dernier pourrait être difficilement projetée à longue distance et diminuer la discrimination faciale de l'anion tosylate. Ceci expliquerait pourquoi le développement de nouveau catalyseurs d'iode hypervalent chiraux et leur constante optimisation n'ont pas porté fruit.

Pour contourner ce problème, il fut proposé au sein du groupe d'utiliser des analogues d'énols isolables qui forceraient l'obtention d'un intermédiaire *C*-lié plutôt que *O*-lié. Ce faisant, l'induction de la chiralité se ferait au moment de l'attaque sur une face ou l'autre de l'énol et permetterait l'atteinte de haut *ee*.

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CHAPITRE 1 : ENOL AND YNOL SURROGATES : PROMISING SUBSTRATES FOR HYPERVALENT IODINE CHEMISTRY

1.1. La réaction d'α-tosyloxylation stéréosélective d'acétates d'énol

La réaction d'α-tosyloxylation d'acétates d'énol de façon racémique puis de façon stéréosélective ont porté fruit et ont été publiés par le docteur ayant fait ces recherches : Benoit Basdevant, Ph.D.

Ces résultats prometteurs ont encouragés le groupe à s'attarder au développement de la chimie d'analogues d'énols pour des réactions d'α-fonctionnalisation, et ont motivé la rédaction d'une revue de littérature sur tout ce qui s'est fait dans le domaine des oxydations d'alcènes riches par des réactifs d'iodes hypervalent. J'ai rédigé la première version de cet article de revue, et j'ai participé activement à sa correction.

1.2. Article

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Asian J. Org. Chem. **2016**, *5*, pp 1078 - 1099

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Abstract: In numerous iodine(III)-mediated methodologies that involve ketone compounds, the enol tautomer is expected to be the reactive species. In this context, the exploration of enol and ynol surrogates as substrates is of great interest. Activated π-systems have been shown to exhibit interesting and highly exploitable behaviour toward hypervalent iodine reagents. This has led to the development of numerous useful oxidative transformations. Enamines, enamides, enol derivatives, haloalkenes and haloalkynes are all enol or ynol surrogates that are reactive towards the most popular iodanes and

iodonium salts. This Focus Review will describe past and on-going research involving these substrates to gain insight on the similarities and disparities observed in their reactivity profiles.

1. Introduction

There is no doubt that hypervalent iodine reagents have been at the forefront of synthetic methodology developments in the past ten years.[1] They have demonstrated rich and useful reactivity profiles in the field of oxidative transformations.[2] Since 2009, our group has worked on the development of stereoselective methods for the α-functionalization of ketone compounds. In the course of this research, we have explored substrates that could act as enol surrogates. As it turns out, this large family of substrates has been studied by numerous researchers. This review aims to describe the achievements and current limitations of these promising compounds. Phenol and aniline derivatives could be comprised into this category. However, numerous reviews have been published on phenol, naphthol, and aniline dearomatization chemistry, and hence this review will not include them.[3] Therefore, the review will focus specifically on enol and ynol surrogates that are not part of aromatic or heteroaromatic substrates.

The review was distributed in subsections according to the nature of the substrates involved in the described methodologies. These subfamilies are illustrated below (Figure 6).

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[1] V. V. Zhdankin, Hypervalent Iodine Chemistry Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds, Wiley, Chichester, **2013**.

[2] (a) M. Uyanik, K. Ishihara, Chem. Commun. **2009**, 2086; (b) T. Wirth, Angew. Chem. Int. Ed. **2005**, 44, 3656; (c) H. Tohma, Y. Kita in Hypervalent Iodine Chemistry (Ed.: T. Wirth), Springer, Berlin, **2003**, p.209; (d) V. V. Zhdankin, Arkivoc **2009**, 1, 1; (e) V. V. Zhdankin, P. J. Stang, Chem. Rev. **2002**, 102, 2523; (f) R. M. Moriarty, O. Prakash, Org. React. **2001**, 57, 327; (g) A. Varvoglis, Hypervalent Iodine in Organic Synthesis Academic Press, San Diego, **1997**.

[3] (a) L. Pouységu, D. Deffieux, S. Quideau, Tetrahedron **2010**, 66, 2235-2261; (b) S. Quideau, L. Pouységu, D. Deffieux, Synlett **2008**, 467–495; (c) S. Rodriguez, P. Wipf, Synthesis **2004**, 2767–2783.

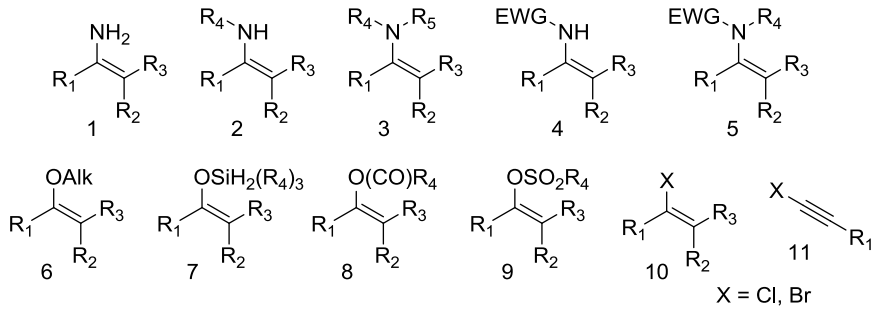


Figure 6. Enol and ynol surrogates families described in this review

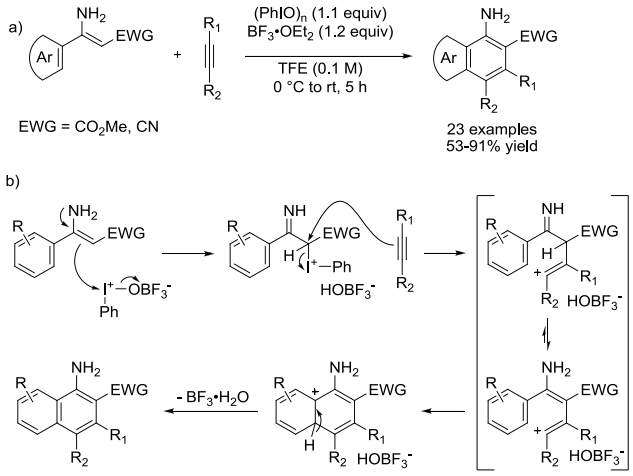
2. Enamines and Enamides Substrates

Amongst all the oxidative rearrangements of substituted alkenes by hypervalent iodine compounds, the ones performed on enamines and enamides have prevailed and have initiated a stream of publications.

2.1. Unsubstituted Enamines (1)

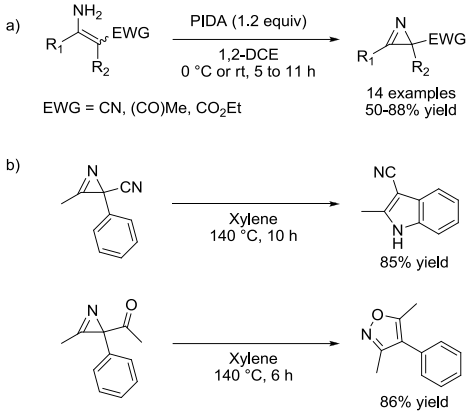
In 2013, Wei and co-worker have developed a methodology in which oxidation of enamine substrates and sequential nucleophilic attack by an alkyne, followed by benzannulation and aromatization yields highly substituted aminonaphthalenes (Scheme 5).[4] The mechanistic proposal is described in Scheme 5b. In accord with the latter, deactivated alkynes such as methyl propiolate led only to trace amounts of aminonaphthalene. It is assumed that alkynes with electron withdrawing groups are slowing the rate of their nucleophilic attack on the iodonium intermediate. On the other hand, moderate to good yields were obtained from aliphatic and aryl terminal alkynes as well as with internal alkynes. Regioselectivity of addition of the alkyne will be determined by the ability of R_1 or R_2 to stabilize the vinylic carbocation. *Meta*-substituted phenyl enamines show low (<2:1) to good (only one isomer) levels of selectivity toward *ortho*-cyclization. The selectivity is greatly enhanced by electron donating groups (*e.g.* OMe) and diminished by electron-withdrawing groups (*e.g.* Cl).

[4] P. Gao, J. Liu, Y. Wei, Org. Lett. **2013**, 15, 2872–2875.



Scheme 5. Methodology developed by Wei and co-workers (a) and proposed mechanism (b)

They have reported an extended study for this synthetic transformation in 2015.[5] In particular, they have demonstrated tolerance of the method toward the presence of an alkyl chain on the enamine nitrogen. In contrast, when a phenyl group is introduced on this nitrogen, only trace amounts of the desired product was observed. They also have given credibility to their proposed mechanism through control experiments, such as the evaluation of kinetic isotopic effect.

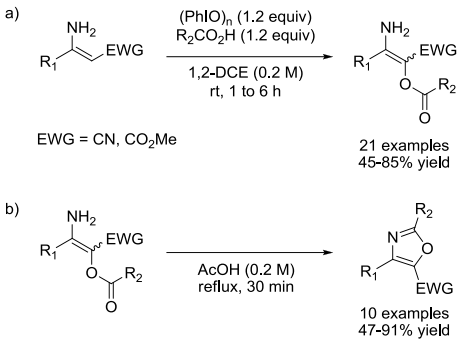


Scheme 6. Methodology developed by Du, Zhao and co-workers (a) and synthetic applications (b)

[5] P. Gao, M. Fan, Z. Bai, Y. Wei, Chin. J. Chem. **2015**, 33, 479–485.

In 2009, Du, Zhao and co-workers have reported the first direct conversion of enamines to 2*H*-azirines promoted by (diacetoxyiodo)benzene (PIDA) as the oxidant (Scheme 6).[6] They demonstrated the synthetic potential of the obtained azirines by promoting their conversion to useful heterocycles by a thermal rearrangement (Scheme 6b).

It was demonstrated in a subsequent related publication that β-acyloxylation of the enamines utilized in their previous study is also a possible outcome, depending on the substitution pattern of the latter (Scheme 7a).[7] The incorporation of a ligand from the iodine(III) oxidant in the final product is a key feature of this transformation. Consequently, they replaced PIDA by an *in situ*-generated (diacyloxyliodo)benzene, obtained from the condensation of various carboxylic acids on iodosylbenzene to broaden the scope of accessible products.



Scheme 7. Acyloxylation of enamines (a) and conversion of products to oxazoles (b)

The latters are used for the synthesis of oxazoles by dehydration. Since the one-pot reaction is described as sluggish, the β-acyloxyenamines are isolated and cyclized in boiling acetic acid (Scheme 7b). Nevertheless, one-pot conditions were developed for the synthesis of enantioenriched oxazoles from enamines and *N*-protected amino acids. This method tolerates some interesting functionalities, such as chloro, alkenyl and protected amines.

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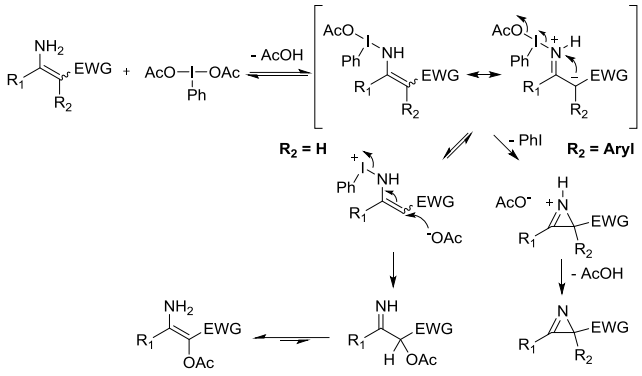
[6] X. Li, Y. Du, Z. Liang, X. Li, Y. Pan, K. Zhao, Org. Lett. **2009**, 11, 2643–2646.

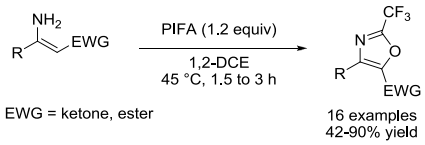
[7] X. Liu, R. Cheng, F. Zhao, D. Zhang-Negrerie, Y. Du, K. Zhao, Org. Lett. **2012**, 14, 5480–5483.



Scheme 8. Proposed mechanism to explain 2*H*-arizine formation and acetoxylation

While the authors proposed a mechanism in the first report to explain azirine formation, a rationale for the competing β-acyloxylation can be put forward (Scheme 8). Azirine formation occurs when R_2 is an aromatic moiety. The increased steric bulk from this group could prevent S_N2' displacement and explain azirine formation. In contrast, when R_2 = H, decreased steric hindrance of the enamine β-carbon could explain facile S_N2' displacement and preference for the acyloxylation pathway. This competing reaction is assumed to occur from intermediate **A**, as it could undergo a S_N2'-type displacement to eject iodobenzene.

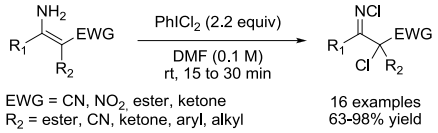
In relation to these two publications, the same group exploited a similar type of chemistry in 2011 to access 2-trifluoromethyloxazoles using [bis(trifluoroacetoxy)iodo]benzene (PIFA) as the oxidant (Scheme 9).[8] The reaction involves a one-pot acid-catalyzed condensation-aromatization cascade. A mechanism similar to the one illustrated in Scheme 8 can be considered to rationalize the products obtained. The reaction scope is broad and shows moderate to very good yields under the optimized conditions (42-90%).



Scheme 9. Synthesis of 2-trifluoromethyloxazoles developed by Du, Zhao and co-workers

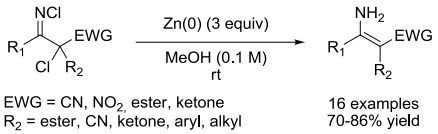
[8] F. Zhao, X. Liu, R. Qi, D. Zhang-Negrerie, J. Huang, Y. Du, K. Zhao, J. Org. Chem. **2011**, 76, 10338–10344.

In 2014, Zhao, Du and co-workers reported a rapid double oxidation of deactivated enamines by (dichloroiodo)benzene in DMF to yield α,*N*-dichloroimines with good to excellent yields (in 15 to 30 minutes at room temperature (Scheme 10).[9] The proposed reaction mechanism is consistent with most λ^3-iodane-mediated enamine oxidations for the first step. The reaction proceeds through an S_N2' type displacement (Scheme 8), despite the fact that R_2 is not hydrogen. This could be explained by the small size of the chloride ion acting as a nucleophile. Since the resulting α-chloro imine cannot tautomerize back to an enamine isomer, it is further oxidized to the α,*N*-dichloroimine.



Scheme 10. Dichlorination of enamines developed by Zhao, Du and co-workers

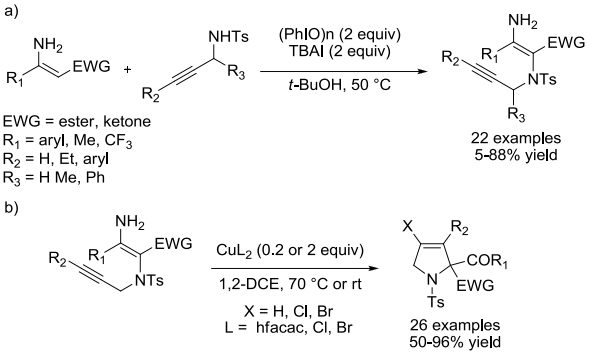
Most enamines described in the reaction scope possess an electron withdrawing group at the R_2 position, but alkyl chains and phenyl groups are also well tolerated. The influence of the nature of R_1 on the yield or reaction time seems very mild and shows no evident trend. Anhydrous conditions are required in order to yield the desired α,*N*-dichloroimine. When wet DMF is used, the corresponding α-chloro ketone is obtained in good yields. It is suggested by the authors that the chloroketone is obtained from the hydrolysis of the α,*N*-dichloroimine *in situ*. The authors also attempted to form the corresponding azirine from a model α,*N*-dichloroimine, without success. They instead developed conditions to reduce the product back to the corresponding enamine substrate (Scheme 11).



Scheme 11. Optimized reductive conditions to convert the dihaloimines to their corresponding enamines

[9] L. Tang, D. Zhang-Negrerie, Y. Du, K. Zhao, Synthesis **2014**, 46, 1621–1629.

In 2015, Fan and co-workers have developed an iodine(III)-promoted oxidative cross-coupling between enamine substrates and propargyl amines.[10] The method enabled the C-N bond formation with a wide range of coupling partners (Scheme 12a). The enamines were oxidized with iodosylbenzene in the presence of tributylammonium iodide (TBAI). It is proposed that TBAI promotes depolymerization of iodosylbenzene. Some of the products obtained (R_3 = H) are used in a subsequent electrophilic cyclization promoted by various copper(II) salts to yield substituted 3-pyrrolines (Scheme 12b).



Scheme 12. Iodine(III)-mediated amination of enamines

2.2. Monosubstituted Enamines (2)

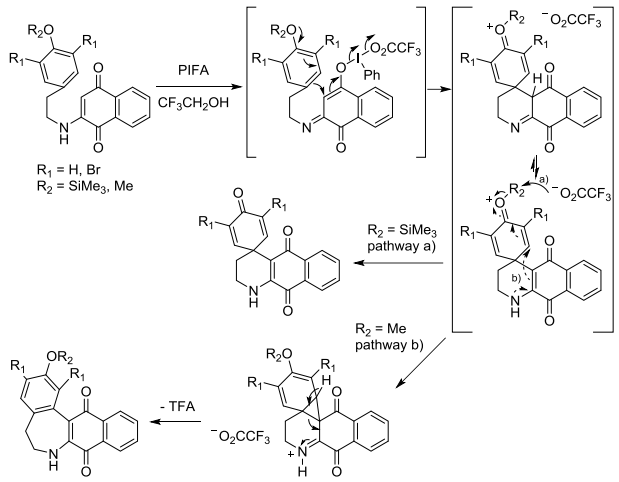
After developing the oxidation of *p*-substituted phenols into spirolactones and *p*-benzoquinone monoacetals using PIFA,[11] Kita and co-workers have applied their methodology for the effective synthesis of azacarbocyclic spirodienone cores.[12] It is a great alternative to the few and ineffective methods of accessing such cores, which was developed to access discorhabdin alkaloids, to enable studies of their antimicrobial and cytotoxic proprieties. The proposed mechanism is initiated by nucleophilic attack of the enamine ketone substrate on PIFA, leading to the displacement of a trifluoroacetate ligand. Nucleophilic attack of the silyl phenol ether on the activated enamine system then occurs. The process is terminated by the desilylation (R_2 = TMS) of the carboxenium ion *via* attack of trifluoroacetate anion (Scheme 13, pathway a). If R_2 is a methyl group, neutralization of the

[10] C. Zheng, Y. Wang, R. Fan, Org. Lett. **2015**, 17, 916–919.

[11] Y. Tamura, T. Yakura, J. Haruta, Y. Kita, J. Org. Chem. **1987**, 52, 3927–3930.

[12] Y. Kita, T. Yakura, H. Tohma, K. Kikuchi, Y. Tamura, Tetrahedron Lett. **1989**, 30, 1119–1120.

carboxenium ion is found to be too difficult. The competing pathway b, involving enamine attack/rearomatization, occurs instead (Scheme 13, pathway b).

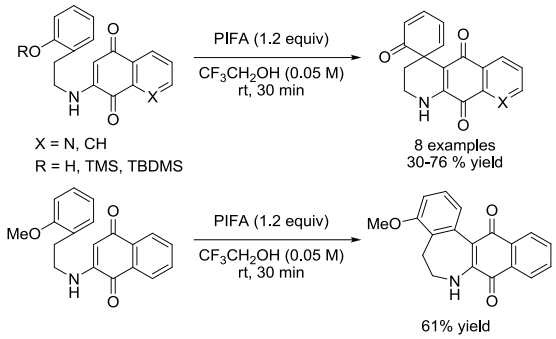


Scheme 13. Synthesis of azacarbocyclic spirodienone and 1*H*-azepine cores

It is worthy to note that this work exemplifies the concept of intramolecular coupling of two tethered nucleophilic moieties using an Umpolung strategy. In this particular case, a silyl phenol ether is tethered to an enamine. The latter is oxidized and rendered electrophilic by PIFA, making it prone to nucleophilic attack by the silyl phenol ether.

The intramolecular cyclization of substituted phenols into azacarbocyclic spirodienones was revisited by Kita and co-workers in 1996.[13] This facile route was explored on *o*-substituted phenols. With the free (R = H) or silylated (R = TMS, TBDMS) phenols, the desired spirodienones are obtained in modest to good yields (Scheme 14).

[13] Y. Kita, T. Takada, M. Ibaraki, M. Gyoten, S. Mihara, S. Fujita, H. Tohma, J. Org. Chem. **1996**, 61, 223–227.

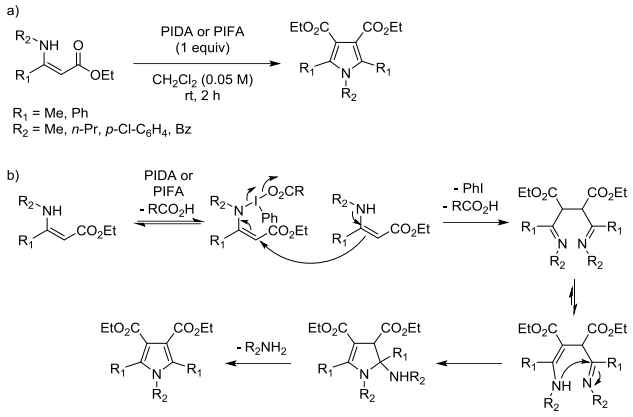


Scheme 14. Synthesis of azacarbocyclic spirodienone cores from o-substituted phenols

The introduction of nitrogen in the aminonaphthoquinone system (X = N) diminished the yield of the transformation (30-51%). This could be caused by the lesser nucleophilicity of the enamine moiety towards PIFA, due to the electron withdrawing effect of the pyridine ring. As observed with the *p*-substituted phenols, the *O*-methylated phenol ether leads to a 1*H*-azepine product, through a mechanism similar to pathway b (Scheme 13).

In 2001 Zhang *et al.* have used PIDA to promote the dimerization of mono-substituted enamine esters to yield symmetric pyrroles.[14] The method supports alkyl (Me, *n*-Pr), aryl (*p*-Cl-C_6H_4), and acyl (Bz) groups on the nitrogen atom and alkyl and aryl groups on the enamine (Scheme 14). The method provides fair to good yields with PIDA (3-7 h, 26-48%), while the use of PIFA offers an increase in yield and shorter reaction times (0.5-3.5 h, 48-87%). The proposed mechanism involves oxidation of the enamine-ester and subsequent nucleophilic attack of an enamine-ester followed by cyclization-aromatization of the dimerization adduct (Scheme 15b).

[14] P.-F. Zhang, Z.-C. Chen, Synth. Commun. **2001**, 31, 1619–1624.



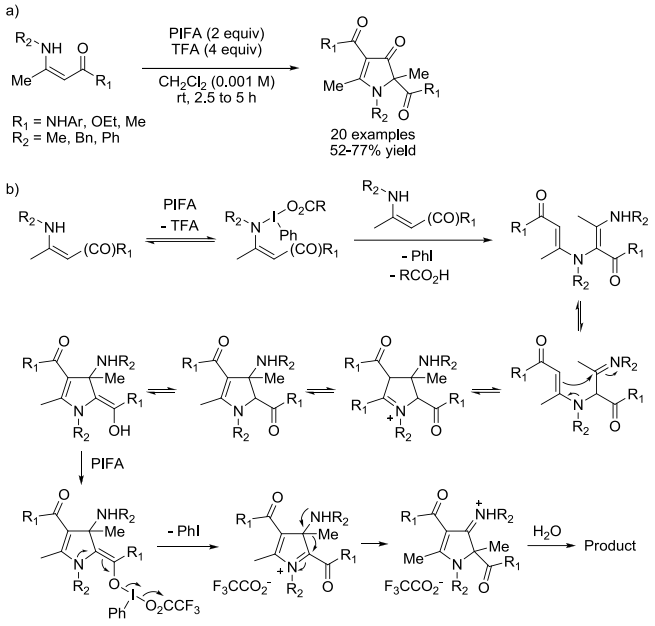
Scheme 15. Iodine(III)-mediated dimerization of enamines to access symmetric pyrroles (a) and proposed mechanism (b)

In the same year, Chen and Zhang have expanded the scope of this synthetic transformation.[15] They have shown that the ester moiety can be replaced by benzoyl and acetyl groups. In 2006, it was shown by Dong and co-workers that, under acidic conditions, the same enamine esters would undergo dimerization with a different regiochemistry.[16] The addition of TFA to the reaction mixture promotes the formation a of C-N bond instead of a C-C bond, which lead to the formation of pyrrolin-4-ones in moderate yields (Scheme 16a).

This transformation either occurs through attack by the nucleophilic carbon of one enamine on the activated nitrogen linked to the hypervalent iodine species, or by the nucleophilic nitrogen of the enamine through a S_N2' type displacement, analog to the mechanism illustrated in Scheme 15b. The asymmetric dimer intermediate can then cyclize and be oxidized further by the second equivalent of PIFA, leading to the observed product upon hydrolysis (Scheme 16b). These examples are particularly interesting as C-C *versus* C-N bond formation sequence is controlled by a simple acid additive.

[15] P.-F. Zhang, Z.-C. Chen, J. Chem. Res. (S), **2001**, 4, 150-152.

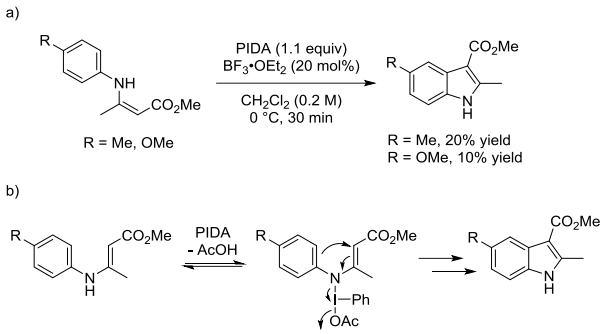
[16] J. Huang, Y. Liang, W. Pan, Yang, D. Dong, Org. Lett. **2007**, 9, 5345–5348.



Scheme 16. Iodine(III)-mediated dimerization of enamines to access pyrrolin-4-ones (a) and proposed mechanism (b)

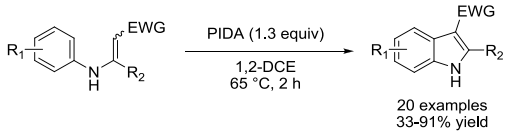
A very similar methodology was published in 2009 by Yu and co-workers.[17] They have tested numerous oxidants, including PIDA, and acid additives to perform the dimerization of enamine esters to obtain symmetric pyrroles. They have found that activation of PIDA with $BF_3{\cdot}OEt_2$ could give results equivalent to those obtained by Zhang and Chen, whom employed PIFA. Moreover, they have explored the synthesis of non-symmetric pyrroles by mixing two enamines. It is also worthy to note that in the case of some enamines bearing an *N*-aryl moiety with an electron-donating group (Ar = *p*-tolyl and *p*-MeO-C_6H_4), indoles products could be obtained in low yields (Scheme 17).

[17] J.-Y. Wang, S.-P. Liu, W. Yu, Synlett **2009**, 2009, 2529–2533.



Scheme 17. Iodine(III)-mediated formation of indoles (a) and proposed mechanism (b)

This strategy to form indoles was also recognized by Du, Zhao and co-workers. They also reported, in 2009, the formation of indoles under thermal conditions from PIDA and *N*-arylated enamines.[18] In contrast to the work of Yu, this work was mainly focused on the access of indoles. Consequently, the scope and yields reported are broader and higher, respectively. From the scope investigation, it was found that only low regioselectivities (<2:1) were achievable for *meta*-substituted aryls (Scheme 18).

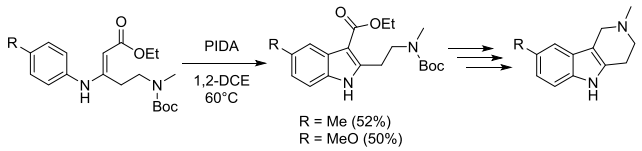


Scheme 18. Iodine(III)-mediated formation of indoles

In 2013, they applied their well-established methodology for the construction of tetrahydro-γ-carboline skeletons via C-C bond formation. These compounds have synthetic and biological relevance (Scheme 19).[19]

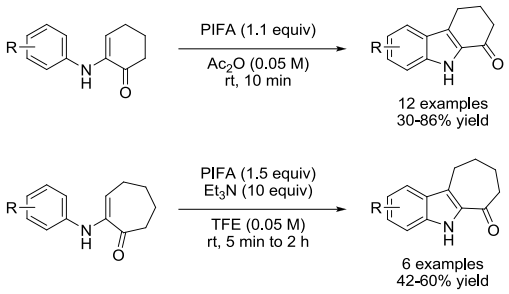
[18] W. Yu, Y. Du, K. Zhao, Org. Lett. **2009**, 11, 2417–2420.

[19] J. Lv, J. Li, D. Zhang-Negrerie, S. Shang, Q. Gao, Y. Du, K. Zhao, Org. Biomol. Chem. **2013**, 11, 1929–1932.



Scheme 19. Iodine(III)-mediated formation of indoles

A year later, they have reported the same type of transformation on new substrates and using PIFA to access substituted tetrahydro-1*H*-carbazol-1-ones and 7,8,9,10-tetrahydrocyclo-hepta[*b*]indol-6(5*H*)-ones (Scheme 20).[20]



Scheme 20. Iodine(III)-mediated formation of indoles

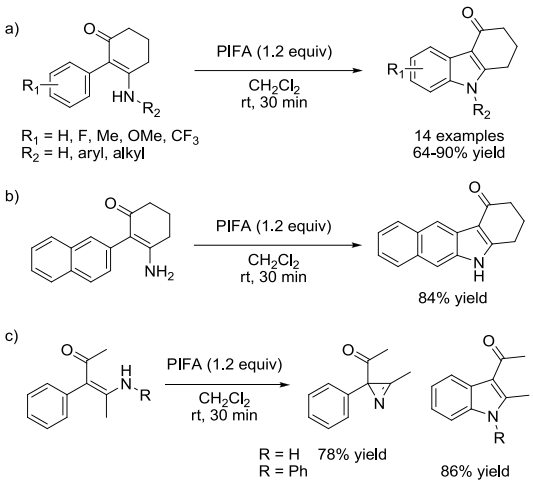
In relation to this work, the use of iodine(III) reagents to promote the conversion of enamines to indoles was previously reported. The success of hypervalent iodine-mediated formation of *N*-containing heterocycles started in 2006 by a series of publications, such as the synthesis of *N*-alkyl and *N*-aryl indoles from β-aryl enamines with PIFA by Zhao and co-workers (Scheme 21).[21] Conceptually the method is similar to the previously described publications, as it involves activation of the enamine with an iodine(III) reagent. In contrast, the activation results in the formation of a C-N bond. The scope is fairly broad and numerous substitution patterns are tolerated on the aromatic group. Unfortunately, this method suffers the same lack of regioselectivity that is observed with *N*-aryl enamines (Scheme 18) with *meta*-substituted aryls.

[20] H. Shi, T. Guo, D. Zhang-Negrerie, Y. Du, K. Zhao, Tetrahedron **2014**, 70, 2753–2760.

[21] Y. Du, R. Liu, G. Linn, K. Zhao, Org. Lett. **2006**, 8, 5919–5922.

Scheme 21. Iodine(III)-mediated formation of indoles

Du, Zhao and co-workers have expanded the scope of their methodology in 2012 to access carbazolones and 3-acetylindoles from cyclic enaminones in moderate to very good yields (Scheme 22).[22]Again, poor regioselectivities were obtained from *meta*-substituted aryls, except for the example involving 2-(2'-napthyl)enaminone (Scheme 22b). Greater yields were obtained from electron poor aryls, such as *p*-nitro-phenyl, than from aryls systems with a higher electron density. This can be owed to a competing side-reaction of electron rich aryls directly with the oxidant. Interestingly, while unsubstituted (NH_2) cyclic enaminones lead to the formation of *N*-unsubstituted carbozolones, the presence of a phenyl moiety on the nitrogen is necessary for acyclic enaminones to prevent azirine formation (Scheme 22c).

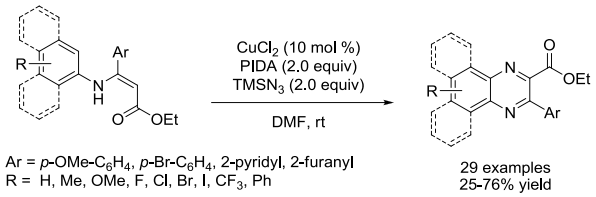


Scheme 22. Synthesis of carbazolones (a,b) and 3-acetylindoles (c)

While both methods for the synthesis of indoles have equivalent scopes and similar limitations in terms of regioselectivities, they are not equivalent in terms of substrates accessibility. The use of *N*-aryl enamines is considered to be more advantageous since they are more readily accessible than *C*-aryl

[22] X. Ban, Y. Pan, Y. Lin, S. Wang, Y. Du, K. Zhao, Org. Biomol. Chem. **2012**, 10, 3606–3609.

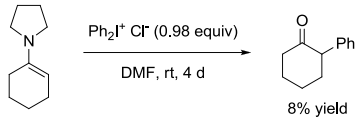
enamines. Additionally, Yu and co-workers expanded the usefulness of *N*-aryl enamines in accessing quinoxaline derivatives through iodine(III)-mediated oxidation of these substrates *via* a novel double oxidative C-N bond formation involving PIDA and trimethysilyl azide (Scheme 23).[23]



Scheme 23. Iodine(III)-mediated formation of quinoxalines

2.3. Disubstituted Enamines (3)

To the best of our knowledge, there exist only a few examples of oxidative rearrangements of disubstituted enamines mediated by iodine(III) reagents. Martin E. Kuehne has published a hypervalent iodine-mediated arylation of enamines to access α-aryl ketones.[24] The disubstituted enamine is submitted to oxidation with a diaryliodonium salt. Reductive coupling to expulse iodobenzene and hydrolysis of the iminium salt yields the desired α-aryl ketone. Unfortunately, despite numerous attempts to optimize the reaction conditions, the transformation led to the desired arylated products in very low yields (Scheme 24).



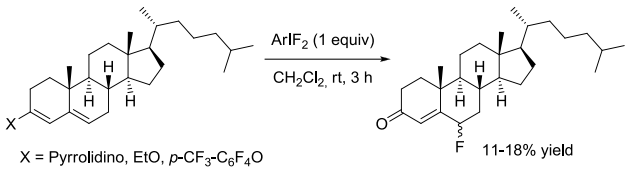
Scheme 24. Arylation of enamines using diaryliodonium salts

Motherwell and co-worker have explored the use of (difluoroiodo)arenes to promote fluorination of nucleophilic enol surrogates, such as enamines and enol ethers. Conceptually, they considered the approach as an alternative to electrophilic fluorine sources, as the nucleophile first would attack the electrophilic iodine(III) reagent. The now activated substrate would then become fluorinated by attack

[23] H. Ma, D. Li, W. Yu, Org. Lett. **2016**, 18, 868–871.

[24] M. E. Kuehne, J. Am. Chem. Soc. **1962**, 84, 837–847.

of a fluoride anion. They envisioned that this strategy could introduce a nucleophilic fluoride at the terminal position of a dienol/dienamine site (Scheme 25).[25]

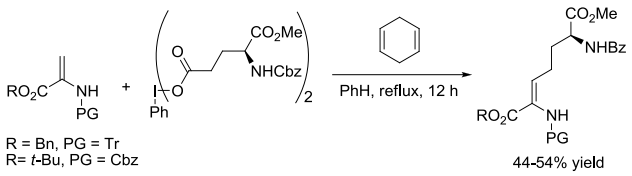


Scheme 25. Arylation of enamines using diaryliodonium salts

Many (difluoroiodo)arenes were synthesized, but (difluoroiodo)*p*-*t*-butybenzene was preferred because of its great stability at -20°C as a crystalline solid. Assessment of the mechanism led to a prevalent proposal in which the oxidation of the dienamine system occurs through a radical process. The method, while plagued with low yields, exhibits features of much interest such as a complete regioselectivity for substitution at the terminal position of the diene. Furthermore, the transformation is expected to be suitable with other substrates by tuning the redox potential of the oxidant by modification of the aromatic ring.

2.4. Monosubstituted Enamides (4)

In 2002, Vederas and Sutherland have reported radical additions to enamides to access diaminopimelic acid analogs.[26] The reactive radical intermediates are generated by homolytic dissociation of an acyloxy ligand and decarboxylation from the illustrated (diacyloxyiodo)benzene (Scheme 26). The latter is obtained by ligand exchange on PIDA with *N*-protected glutamate ester.

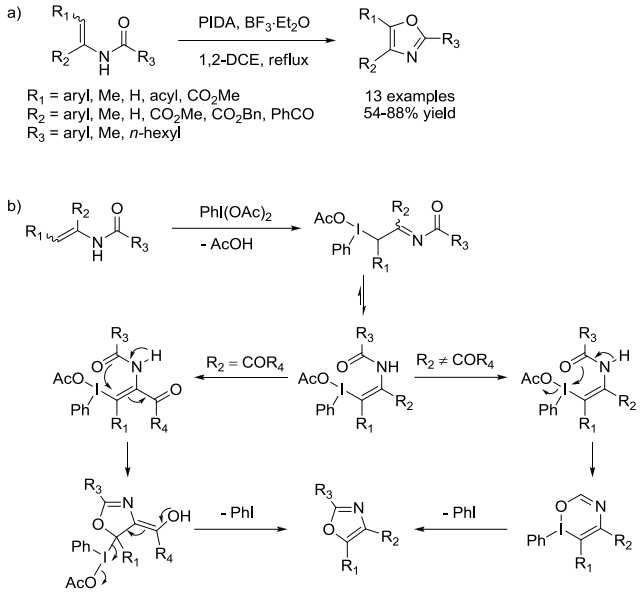


Scheme 26. Addition of radicals to enamides, generated from iodanes

[25] J. J. Edmunds, W. B. Motherwell, J. Chem. Soc., Chem. Commun. **1989**, 881–883.

[26] A. Sutherland, J. C. Vederas, Chem. Commun. **2002**, 224–225.

Du, Zhao and co-workers have once again exemplified the utility of (diacyloxyiodo)benzene for the formation of carbon-heteroatom bonds, under conditions free of metal catalysts, by developing a method to access fully substituted oxazoles from enamides by C-O bond formation utilizing PIDA under Lewis acid activation (Scheme 27a).[27]



Scheme 27. Synthesis of oxazoles from *N*-acyl enamides

Reaction optimization showed the need for an excess of Lewis acid, $BF_3 \cdot OEt_2$, to achieve high yields. This result is consistent with the necessity to form an activated iodonium intermediate to favor ligand exchange with the substrate, as illustrated by our group in a recent experimental/computational study.[28] The Lewis acid could also facilitate imine-enamine tautomerism in the various reaction processes. The mechanism could proceed through numerous intermediates (Scheme 27b). A year later, Nachsheiem and Hempel have published other conditions to yield 2,5-disubstituted oxazoles from similar substrates, in low to good yields (Scheme 28a).[29] They exploited an alternative activation strategy, using TMSOTf with PIFA to enhance its activity. They proposed, in their mechanism, the formation of the more reactive [bis(triflyl)iodo]benzene species. The stoichiometry of TMSOTf is important; if only a slight excess is used with PIDA, it is possible to isolate oxazoline intermediates (Scheme 28b). Treatment of

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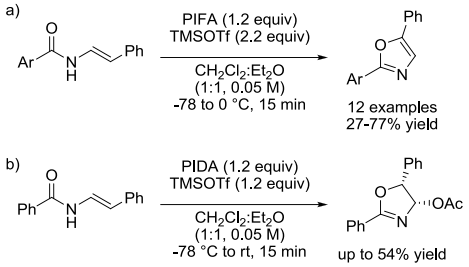
[27] Y. Zheng, X. Li, C. Ren, D. Zhang-Negrerie, Y. Du, K. Zhao, J. Org. Chem. **2012**, 77, 10353–10361.

[28] A. Jobin-Des Lauriers, C. Y. Legault, Molecules **2015**, 20, 22635–22644.

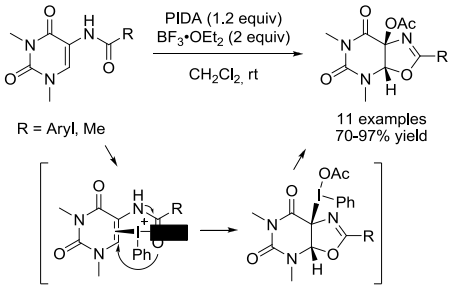
[29] C. Hempel, B. J. Nachtsheim, Synlett **2013**, 2013, 2119–2123.

the latter with another equivalent of TMSOTf then leads to the formation of the corresponding 2,5-diaryloxazole.



Scheme 28. Synthesis of oxazolines and oxazoles

In 2014, the cyclization of uracil derivatives into fused oxazoline-uracil compounds was accomplished in high yields by Roy and co-workers by Lewis acid-activated PIDA-mediated oxidation.[30] Optimization of the reaction conditions led to excellent yields for a range of aryl substituents (Scheme 29). Yields and reaction rates seem to be lowered by aryls with electron withdrawing groups, and enhanced by electron rich aromatics. The yield suffers from an alkyl (i.e. R = Me) substituent. Interestingly, a *syn* acetoxy-hydrogen relation is observed on the bicyclic bridge, pointing toward a final reductive elimination step in the reaction process (Scheme 29).



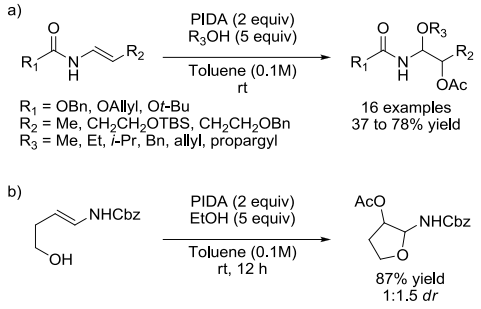
Scheme 29. Synthesis of oxazolines and oxazoles

Masson and co-workers have reported in 2013 that α-acetoxy aminals could be accessed from monosubstituted enecarbamates by α-acyloxylation using PIDA in toluene in the presence of an excess of an alcohol. [31] The method supports numerous carbamates, enamine substituents, and alcohols as nucleophiles (Scheme 30). However, the diastereoselectivities observed are very low (<2.2:1 *dr*). An

[30] B. Mondal, S. Hazra, K. Naktode, T. K. Panda, B. Roy, Tetrahedron Lett. **2014**, 55, 5625–5628.

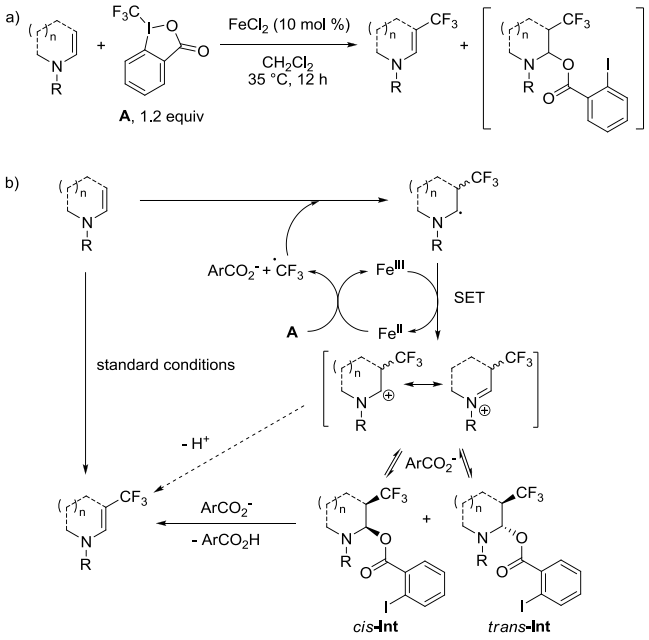
[31] M. Bekkaye, Y. Su, G. Masson, Eur. J. Org. Chem. **2013**, 2013, 3978–3982.

example of an intramolecular trapping by a tethered alcohol to yield cyclic α-carbamido-β-acetoxytetrahydrofuran was made (Scheme 30b).



Scheme 30. Synthesis of oxazolines and oxazoles

In 2015, Gillaizeau and co-workers have introduced new conditions to perform oxidative C-C bond formation.[32] Togni's reagent was used to perform an iron-catalyzed radical trifluoromethylation of deactivated *N*-protected enamines and enamides (Scheme 31a).

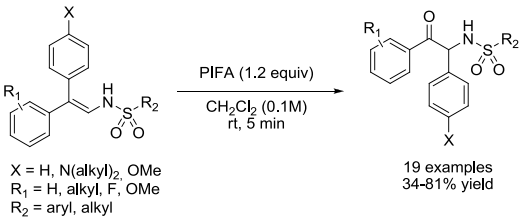


Scheme 31. a) Trifluoromethylation of enamides. b) Proposed mechanism

[32] R. Rey-Rodriguez, P. Retailleau, P. Bonnet, I. Gillaizeau, Chem. - Eur. J. **2015**, 21, 3572–3575.

The proposed radical process (Scheme 31b) is supported by radical inhibition experiments. Intermediates *trans*-**Int** could be isolated and its structure was confirmed by X-Ray. The reported scope is large and proves the broad applicability of this trifluoromethylation methodology.

In 2015, Anbarasan and Yadagiri have reported a method showcasing an oxidative hydrolysis of *N*-sulfonyl-β,β-diarylenamines into α-amino ketones through semi pinacolic-type 1,2-aryl migration (Scheme 32).[33] While the formation of an indole could be expected from such conditions and substrates, this behaviour is reminiscent of other 1,2-aryl migrations mediated by a λ^3-iodane to afford α-aryl ketones.[34] Several sulfonyl groups are tolerated. The rearrangement requires, at least, one aryl group to be electron rich.



Scheme 32. Rearrangement of *N*-sulfonyl enamides.

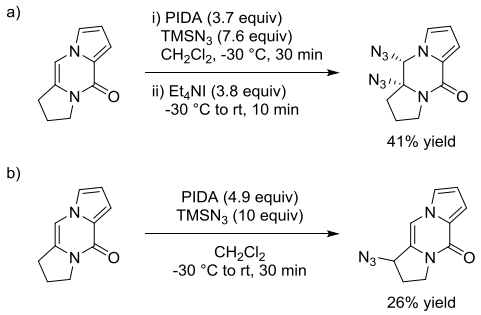
2.4. Disubstituted Enamides (5)

Disubstituted enamides have mostly been used in conjunction with hypervalent iodine reagents for the introduction of one or two nucleophiles such as the work reported by Masson and co-workers.31 Austin and co-workers have reported the diazidation of a pyrazinone structure for the synthesis of (±)-Dibromophakellstatin.[35] Different oxidative conditions were tested, and the best result was obtained with the *in situ* formation of $^{-}I(N_3)_2$ from PIDA, $TMSN_3$, and Et_4NI (Scheme 33a). When hypervalent reagent $PhI(N_3)_2$ was employed, *allyl*-azide was obtained selectively in poor yield (Scheme 33b). This behaviour has some similarities to the methods developed with silyl enol ethers that will be discussed in section 3.2

[33] D. Yadagiri, P. Anbarasan, Chem. Commun. **2015**, 51, 14203–14206.

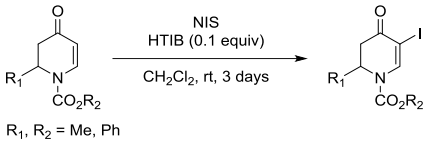
[34] M. Brown, R. Kumar, J. Rehbein, T. Wirth, Chem. - Eur. J. **2016**, 22, 4030–4035.

[35] R. Chung, E. Yu, C. D. Incarvito, D. J. Austin, Org. Lett. **2004**, 6, 3881–3884.



Scheme 33. Azidation of a pyrazinone structure

Comins, Joseph and co-workers have reported in 1995 the iodination of 2,3-dihydropyridones using [hydroxy(tosyloxy)-iodo]benzene (HTIB) in a catalytic process, with NIS as an oxidant and a source of iodide (Scheme 34).[36] Their method was based on the work of McNelis and co-workers on propargyl alcohols.[37] Ten years later, Comins, Kuethe and co-workers exploited this methodology for the synthesis of dienes investigated in numerous Diels-Alder reactions.[38]



Scheme 34. Azidation of a pyrazinone

Lastly, in a series of three publications Dodd and co-workers have demonstrated the versatility of the reaction of PIDA with disubstituted enamides (Scheme 35). [39,40,41] They were able to access α-halo and

[36] D. L. Comins, S. P. Joseph, X. Chen, Tetrahedron Lett. **1995**, 36, 9141–9144

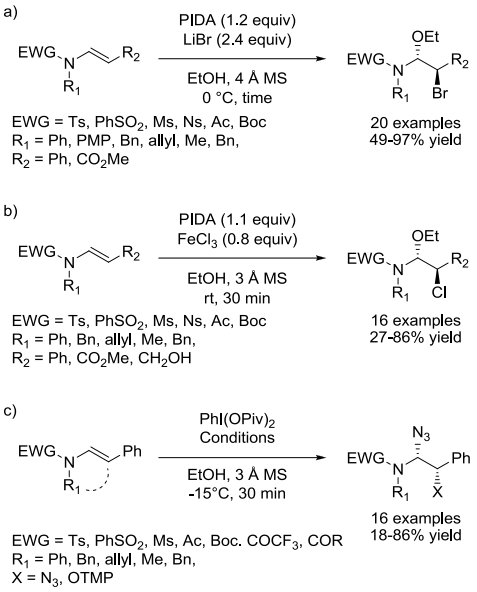
[37] (a) P. Bovonsombat, G. J. Angara, E. Mc Nelis, Tetrahedron Lett. **1994**, 35, 6787–6790; (b) G. J. Angara, E. McNelis, Tetrahedron Lett. **1991**, 32, 2099–2100.

[38] D. L. Comins, J. T. Kuethe, T. M. Miller, F. C. Février, C. A. Brooks, J. Org. Chem. **2005**, 70, 5221–5234.

[39] S. Nocquet-Thibault, P. Retailleau, K. Cariou, R. H. Dodd, Org. Lett. **2013**, 15, 1842–1845.

[40] S. Nocquet-Thibault, C. Minard, P. Retailleau, K. Cariou, R. H. Dodd, Tetrahedron **2014**, 70, 6769–6775.

α-azide aminals by doing the reaction in ethanol. In analogy to the results of Masson and co-workers (Scheme 30), they have obtained poor diasteroselectivities (<3:1) in favor of an *anti*-relation in the process.



Scheme 35. Formation of α-substituted aminals from enamides

3. Enol Substrates

3.1. Alkyl enol ethers (6)

Alkyl enol ethers and their analogues have been exploited along with trivalent iodanes for the introduction of nucleophiles on their nucleophilic carbon. This Umpolung substitution strategy is common with hypervalent iodine reagents; the latter acts as an electrophile toward the enol nucleophilic site, making the carbon to which it is newly bonded prone to substitution by another nucleophile. In most reactions, it is the iodane intermediate's ligand (or iodonium's counterion) that is introduced. Depending on the nature of the enol derivatives (silyl, alkyl and stannyl) and their substitution pattern, this double-substitution allows access to a wide variety of functionalized alkenes and ketones.

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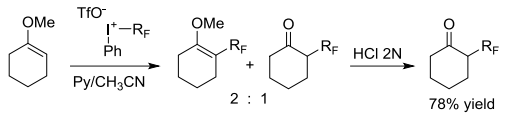
[41] S. Nocquet-Thibault, A. Rayar, P. Retailleau, K. Cariou, R. H. Dodd, Chem. - Eur. J. **2015**, 21, 14205–14210.

Few iodine(III)-mediated C-C bond formations have been reported on alkyl enol ethers. Umemoto and co-workers have used perfluoroalkyl(aryl)-iodonium salts to introduce perfluoroalkyls groups on methyl enol ethers.[42] The addition of the enol ether on the iodonium is followed by re-enolisation to afford a mixture of the perfluoroalkyl substituted enol ethers and α-perfluoroalkylated ketone (Scheme 36). Treatment of the perfluorosubstituted enol and dienol ethers in a diluted aqueous HCl results in the formation of the corresponding α-perfluoroalkyl ketones and γ-perfluoroalkyl enones in good yield.

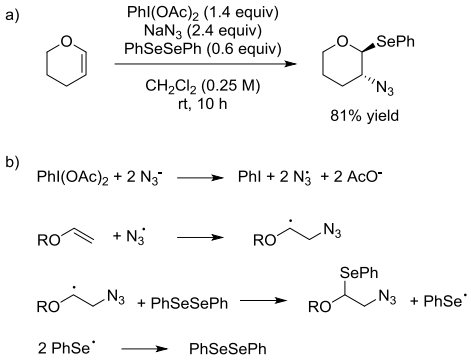


Scheme 36. Reaction of enol ethers with perfluoroalkyl(aryl)iodonium salts

Iodine(III)-mediated C-N bond formations have been more common. The iodine(III)-mediated azidation of enol ethers has been particularly studied. Tingoli *et al.* reported in 1991 the PIDA-promoted azido-phenylselenylation of double bonds.[43] The method affords fair to very good yields and supports aryl, ketone, and ester functional groups. Only one example of enol ether is however reported (Scheme 37a). While the reaction is promoted by PIDA, experimental evidence suggests that it will not directly interact with the alkene, but instead oxidize the azide anion to the azide radical, the active species in the process. Recoupling of PhSe radicals is proposed to explain the fact that the reaction can be completed with a substoichiometric quantity of PhSeSePh (Scheme 37b).

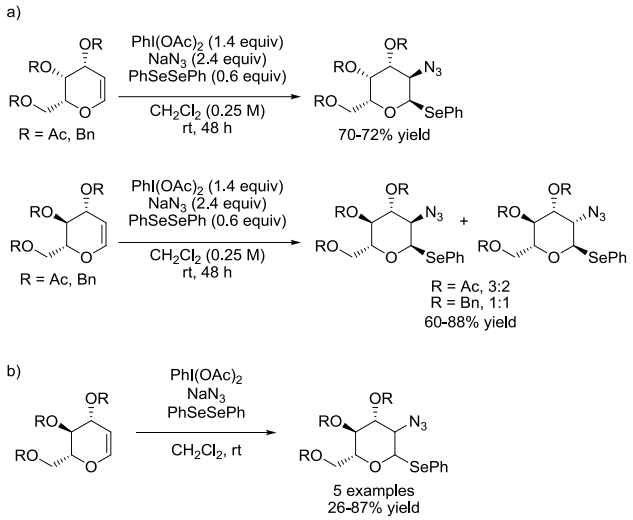
[42] T. Umemoto, Y. Kuriu, S. Nakayama, O. Miyano, Tetrahedron Lett. **1982**, 23, 1471–1474.

[43] M. Tingoli, M. Tiecco, D. Chianelli, R. Balducci, A. Temperini, J. Org. Chem. **1991**, 56, 6809–6813.



Scheme 37. a) Azido-phenylselenylation of enol ethers. b) Proposed mechanism

Two years later Czernecki *et al.* have exploited this methodology to access functionalized glycoside derivatives (Scheme 38a).[44] The same transformation on similar glycols was published only months apart by Santoyo-González and co-workers (Scheme 38b).[45]



Scheme 38. a) Work of Czernecki *et al.* b) Work of Santoyo-Gonzales *et al.*

Nifantiev and co-workers optimized in 2004 the azido-phenylselenylation reaction conditions to make it suitable for large scale production.[46] Owing the lower yields to the poor solubility of sodium azide, they

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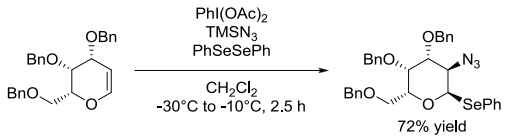
[44] S. Czernecki, D. Randriamandimby, Tetrahedron Lett. **1993**, 34, 7915–7916.

[45]F. Santoyo-González, F. G. Calvo-Flores, P. Garcia-Mendoza, F. Hernández-Mateo, J. Isac-Garcia, R. Robles-Diaz, J. Org. Chem. **1993**, 58, 6122–6125.

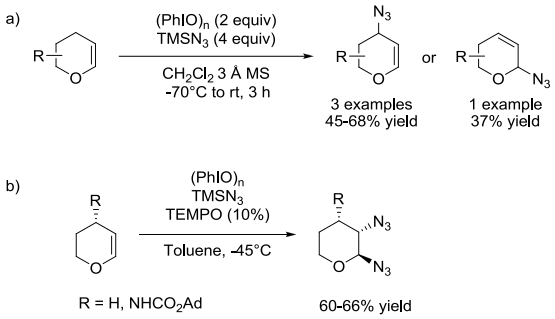
[46] Y. V. Mironov, A. A. Sherman, N. E. Nifantiev, Tetrahedron Lett. **2004**, 45, 9107–9110.

used the more soluble trimethylsilyl azide to achieve homogeneity (Scheme 39). This modification effectively permitted access to higher yields on gram scale reactions. Additionally, shorter reaction times were attained.



Scheme 39. Azido-phenylselenylation protocol developed by Nifantiev and co-workers

In 1995, based on the work of Magnus on silyl enol ethers,[47] Kirschning *et al.* have developed a protocol to rapidly access 3-azidoglycals.[48] The method supports the presence of acetyl, silyl, and benzoyl groups on the starting 3-deoxyglycals, but the yields remain modest (Scheme 40a). A year later Magnus and Roe have demonstrated that the addition of a catalytic quantity of TEMPO to the reaction could drastically change the outcome of the process and promote the diazidation of cyclic enol ethers (Scheme 40b).[49]



Scheme 40. a) Direct azidation of 3-deoxyglycals. b) Diazidation of 3-deoxyglycals

There are fewer reports of iodine(III)-mediated C-O bond formation on alkyl enol ethers. In 1984, Moriarty and co-workers have published a brief communication in which they show preliminary results on the reactivity of natural flavonoids towards PIDA in basic methanol solution (Scheme 41).[50]

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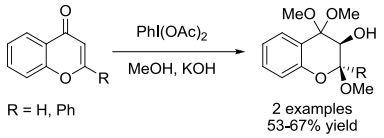
[47] P. Magnus, J. Lacour, J. Am. Chem. Soc. **1992**, 114, 767–769.

[48] A. Kirschning, S. Domann, G. Dräger, L. Rose, Synlett **1995**, 1995, 767–769.

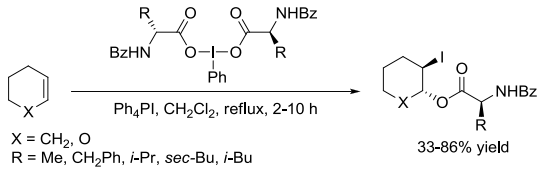
[49] P. Magnus, M. B. Roe, Tetrahedron Lett. **1996**, 37, 303–306.

[50] R. M. Moriarty, O. Prakash, W. A. Freeman, J. Chem. Soc., Chem. Commun. **1984**, 927–929.



Scheme 41. Reaction of flavonoids with PIDA in basic medium

In 2004, Zhdankin and co-workers have developed the iodoacyloxylation reaction of cyclic enol ethers and cyclic alkenes by oxidation of the double bond using chiral *bis*acyloxyiodobenzene reagents.[51] The latter were prepared by ligand exchange from commercially available PIDA and different *N*-protected amino acids in fair yields (68-89%). These reagents were used alongside Ph_4PI, a source of nucleophilic iodide, to afford functionalized amino acid esters in yields from 33% to 86% (Scheme 42). While excellent *trans* selectivity was observed on the alkene addition, the reaction did not show any diastereoselectivity increase arising from the reagent's chirality. The obtained products have a known use as building blocks in the synthesis of analogues of *trans*- and *cis*-glycols.

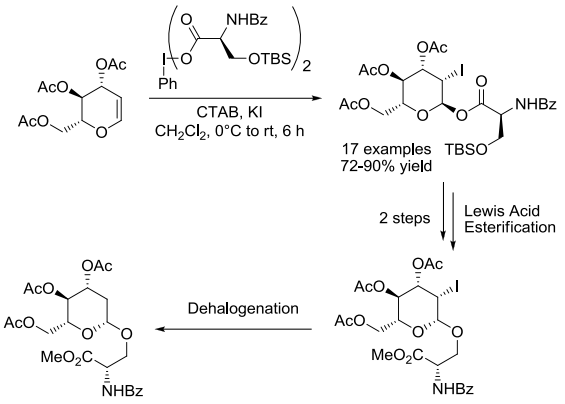


Scheme 42. Reaction of cyclic enol ethers with chiral bisacyloxyiodobenzenes

In 2014, Islam and co-workers have used a similar methodology to functionalize glycals with hypervalent iodine reagents.[52] By treating acetylated glycals with a chiral *bis*acyloxyiodobenzene derived from a protected serine amino acid in the presence of nucleophilic iodide, acyloxyiodination of the double bond in a *trans*- fashion was achieved (Scheme 43).

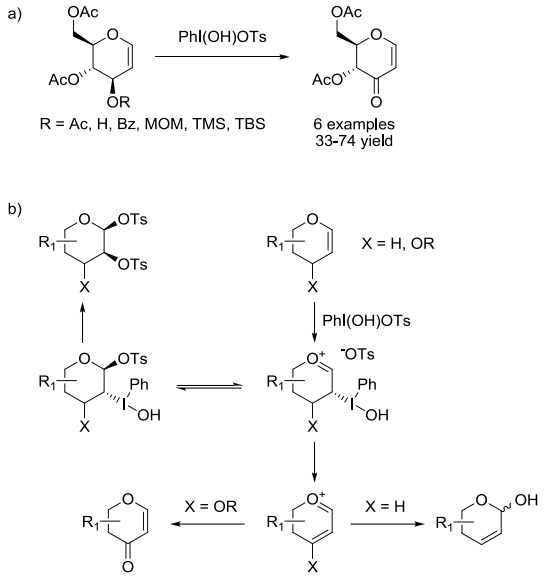
[51] A. Y. Koposov, V. V. Boyarskikh, V. V. Zhdankin, Org. Lett. **2004**, 6, 3613–3615.

[52] M. Islam, N. D. Tirukoti, S. Nandi, S. Hotha, J. Org. Chem. **2014**, 79, 4470–4476.



Scheme 43. Reaction of glycals with a chiral bisacyloxyiodobenzene

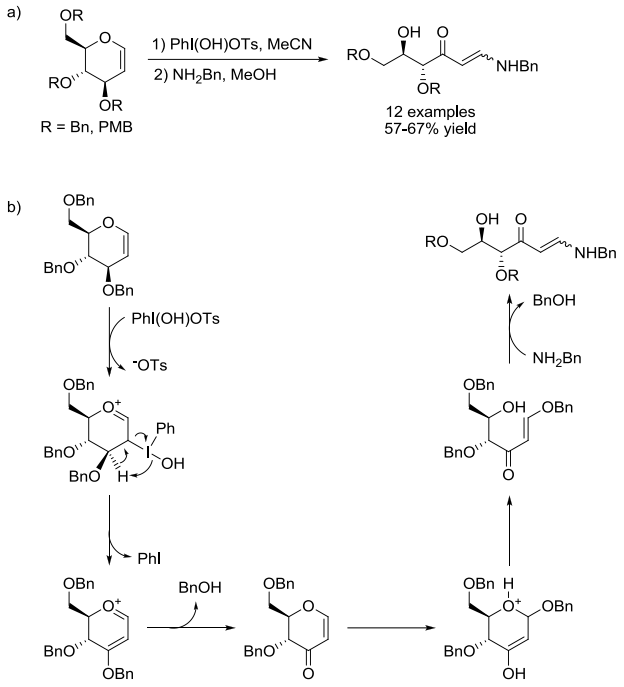
There are also reports of iodine(III)-mediated oxidation of alkyl enol ethers. In 1995, Kirschning has proven the utility of HTIB in the formation of 2,3-dihydro-4*H*-pyranone from glycals in moderate yields (Scheme 44a).[53] The proposed mechanism is initiated by the formation of a *C*-bonded iodane intermediate and finished by dealkylation of the enonium cation to afford the desired 2,3-dihydro-4*H*-pyranone (Scheme 44b). If the X substituent is a hydrogen atom, the enium cation is converted to the corresponding enal hemi-acetal during work-up.



Scheme 44. a) Reaction of glycals with HTIB. b) proposed mechanism

[53] A. Kirschning, J. Org. Chem. **1995**, 60, 1228–1232.

In 2010, following up on Kirschning's work, Lin and co-workers have achieved an oxidative ring opening of a dihydropyrane with HTIB.[54] β-enamino ketones were obtained in yields from 57% to 67% from fully protected glycals (Scheme 45a). In contrast to the results of Kirschning, the β-alkoxyvinyl ketones, and not the pyranones, are isolated following the first step. The mechanism proposed by the authors is illustrated in Scheme 45b.



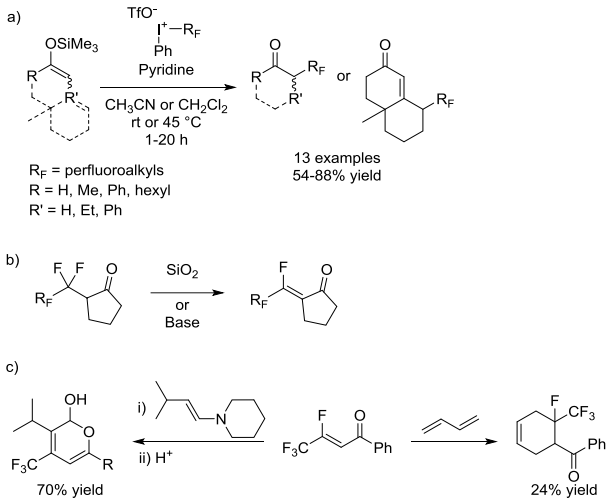
Scheme 45. a) Reaction of glycals with HTIB. b) Proposed mechanism

3.2. Silyl and Stannyl enol ethers (7)

The investigation of C-C bond forming methodologies has been more active with silyl enol ethers. For example, the synthetic method developed by Umemoto and co-workers on alkyl enol ethers, presented in section 3.1, was mainly developed for silyl enol ethers.[42] In contrast to the former, the silyl enol ethers were found to desilylate readily following reaction with the iodonium salts (Scheme 46a). Consequently, the α-perfluoroalkylated ketone products were obtained directly, even under anhydrous conditions. It is interesting to note that the reaction also proceeds with vinylogous enol ethers.

[54] Z.-P. Lin, H.-H. Wu, M. Kimura, K. Kaneko, H. Takayama, F. F. Wong, J. B. Wu, H.-C. Lin, Tetrahedron Lett. **2010**, 51, 5996–5999.

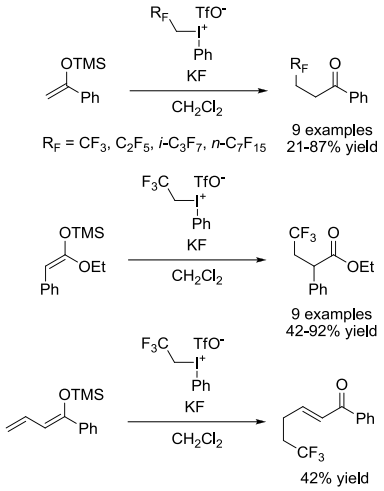
Numerous iodonium sulfonate and triflate salts bearing perfluoroalkyl chains of varying lengths reacted well towards a variety of silyl enol ethers. Functional groups tolerance was not explored, as mostly aliphatic systems were presented in the investigation. Additionally, elimination of HF was found to be easy using a base or was partially observed during purification by silica-gel chromatography, leading to the formation of synthetically useful β-fluoroenones (Scheme 46b). They demonstrated the synthetic utility of these β-fluoro enones in polar reactions with enamines and Diels-Alder reactions (Scheme 46c).



Scheme 46. a) Reaction of silyl enol ethers with perfluoroalkyl-(phenyl)iodonium salts. b) β-Fluoro enones formation. c) Synthetic utility of β-fluoroenones

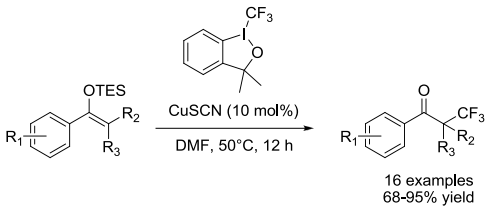
A few years after, Umemoto and co-workers have expanded their previously established methodology to access 1*H*,1*H*-perfluoroalkylated ketones.[55] By submitting silyl enol and dienol ethers to oxidative coupling with (1*H*,1*H*-perfluoroalkyl)phenyl-iodonium tosylate, the corresponding β- and δ-trifluoromethyl ketones and their longer perfluoroalkyl chain analogues were obtained in moderate to high yields (Scheme 47). As seen in their previous methodology (Scheme 46), coupling occurs selectively at the terminal carbon of vinylogous enol ethers. It is interesting to note however that KF is used as an additive instead of pyridine. The method is compatible with ketene trimethylsilyl acetals.

[55] T. Umemoto, Y. Gotoh, Bull. Chem. Soc. Jpn. **1987**, 60, 3823–3825.



Scheme 47. Reaction of silyl enol ethers with 1*H*,1*H*-perfluoroalkyl-(phenyl)iodonium salts

In 2014, Guo and co-workers have developed a methodology for the trifluoromethylation of silyl enol ethers using Togni's reagent and a catalytic quantity of a Cu(I) salt.[56] The proposed mechanism involves the formation of the CF_3 radical by SET between Cu(I) and Togni's reagents, similar to the mechanism proposed in Scheme 31b. A broad scope investigation is reported (Scheme 48).

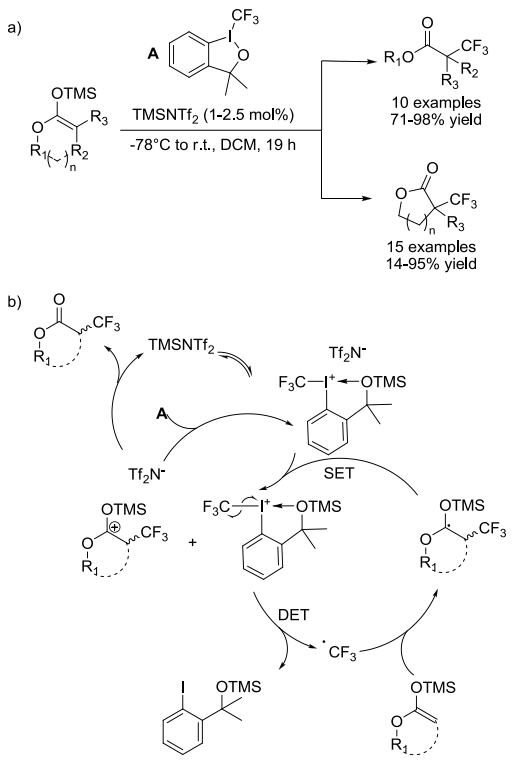


Scheme 48. Copper(I)-catalyzed trifluomethylation of silyl enol ethers

Recently, Togni and co-workers published a variant of Umemoto's methodology that provides access to quaternary α-trifluoromethylated esters and lactones in generally high yields (Scheme 49a).[57]

[56] L. Li, Q.-Y. Chen, Y. Guo, J. Org. Chem. **2014**, 79, 5145–5152.

[57] D. Katayev, V. Matoušek, R. Koller, A. Togni, Org. Lett. **2015**, 17, 5898–5901.

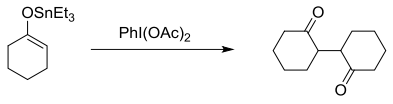


Scheme 49. a) Trifluoromethylation of ketene silyl acetals. b) Proposed mechanism

The reaction yield is barely affected by steric hindrance, but strongly affected by the electronic density of the ketene silyl acetal (KSA) double bond. Addition of a catalytic amount of $TMSNTf_2$ increases the yield dramatically for most compounds. The method was found to be mild and sufficiently selective that alkenes are tolerated as functional groups on the substrates. The reaction mechanism proposed by the authors involves a radical process where $TMSNTF_2$ first promotes silylation and dissociation of the alkoxy ligand of the trifluoromethylating reagent. A single electron transfer (SET) then occurs between this activated iodonium intermediate and the KSA. This promotes the homolytic dissociation and formation of the CF_3 radical. The latter adds to the KSA π-bond. The resulting stabilized radical intermediate then proceeds to do a SET on an activated iodonium intermediate, thus promoting the radical chain and becoming a silylating agent to promote further activation of the trifluoromethylating reagent (Scheme 49b).

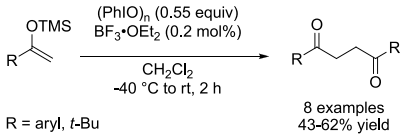
The previously described methodologies involve the reaction of the enol ethers with electrophilic or radical species generated from the iodine(III) reagents. Alternatively, one can consider converting the enol ether to an electrophilic intermediate and trapping it with a nucleophile. Such strategy was first

reported in 1982, with the dimerization reaction of a stannyl enol ether promoted by PIDA (Scheme 50).[58]



Scheme 50. PIDA-mediated stannyl enol ether dimerization

Three years later, Moriarty and co-workers have reported preliminary results to apply this strategy to silyl enol ethers.[59] They then reported the synthetic details in 1987.[60] They used $BF_3 \cdot OEt_2$-depolymerized iodosobenzene as the oxidant (Scheme 51). Only monosubstituted trimethylsilyl enol ethers, bearing non-enolizable groups, were tested for the dimerization reaction. The dimers were all obtained in low to fair yields. They reported one cross-coupling attempt by doing sequential addition of two different silyl enol ethers, but the desired product was obtained in only low yield (27%) with the two possible homodimers (33% combined yields).



Scheme 51. Iodine(III)-mediated dimerization of silyl enol ethers

A year later, Caple, Zefirov and co-workers reported a similar silyl enol ether activation procedure, but extended its reaction to numerous alkene nucleophiles (Scheme 52).[61] They used HBF_4-depolymerized iodosobenzene as the oxidant. The cross-coupling procedure involves the generation of the iodonium

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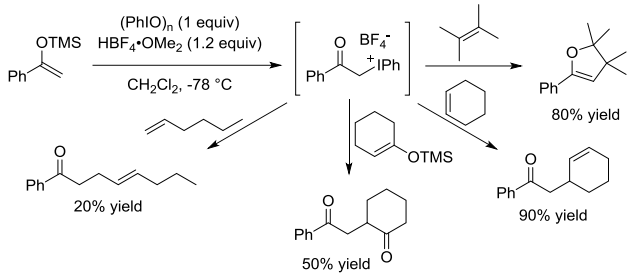
[58] A. N. Kashin, M. L. Tulchinskii, N. A. Bumagin, I. P. Beletskaya, O. A. Reutov, J. Org. Chem. USSR **1982**, 18, 1390–1395.

[59] R. M. Moriarty, O. Prakash, M. P. Duncan, J. Chem. Soc., Chem. Commun. **1985**, 420.

[60] R. Moriarty, O. Prakash, M. P. Duncan, J. Chem. Soc. Perkin Trans. 1 **1987**, 559–561.

[61] V. V. Zhdankin, R. Tykwinski, R. Caple, B. Berlung, A. S. Koz'min, N. S. Zefirov, Tetrahedron Lett. **1988**, 29, 3703–3704.

salt derived from the silyl enol ether at -78 °C, then addition of the alkene nucleophile. The iodonium salt was found to be stable for a few hours at -50 to -20 °C. They also reported the same year a dimerization reaction similar to that of scheme 48, but with the use of the first reported μ-oxo-bridged iodosobenzene tetrafluoroborate, formed from PIDA, tetrafluoroboric acid, and water.[62] The silyl enol ethers derived from acetophenone and cyclohexanone were successfully dimerized, but no yields were reported. Other acids were investigated to activate PIDA, but no yields were again given.[63] In 1989 they reported a full paper with a more extensive investigation of the reaction scope of the work presented in scheme 52, including reaction with an allyl silane.[64]



Scheme 52. Iodine(III)-mediated reaction of silyl enol ethers with alkenes

These interesting C-C bond formation methodologies did not receive much attention for many years. In 1997, Moriarty, Prakash and co-workers have reported a study on the iodine(III)-mediated allylation of silyl enol ethers. The method supports steric hindrance on the enol ether, enabling the formation all-carbon quaternary center, and is compatible with trimethylsilyl ketene acetals (Scheme 53). Interestingly, if the enol ether is first added to the activated iodine(III) reagent, only dimerization of the former is observed. Initial addition of the allyl silane is thus necessary to obtain the desired allylation product.[65] In essence, the enol ether is thought to act as a nucleophile on an electrophilic allylic iodonium species. In analogy to this work, Quideau *et al.* have reported in 1999 the addition of allyl

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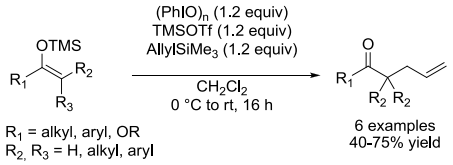
[62] V. V. Zhdankin, R. Tykwinski, R. Caple, B. Berlung, A. S. Koz'min, N. S. Zefirov, Tetrahedron Lett. **1988**, 29, 3717–3720.

[63] V. V. Zhdankin, R. Tykwinski, B. Berglund, M. Mullikin, R. Caple, N. S. Zefirov, A. S. Koz'min, J. Org. Chem. **1989**, 54, 2609–2612.

[64] V. V. Zhdankin, M. Mullikin, R. Tykwinski, B. Berglund, R. Caple, N. S. Zefirov, A. S. Koz'min, J. Org. Chem. **1989**, 54, 2605–2608.

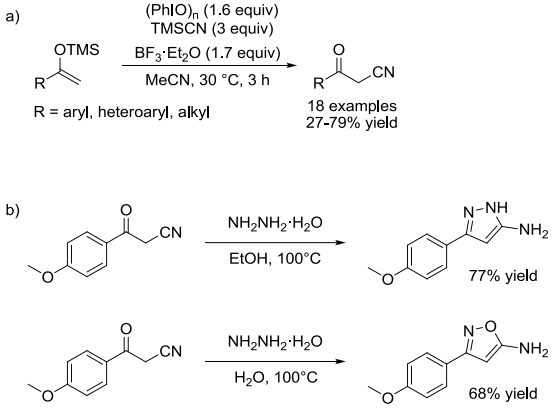
[65] R. M. Moriarty, W. R. Epa, O. Prakash, J. Chem. Res., Synop. **1997**, 262–263.

silane and a vinylogous silyl enol ether on phenoxonium intermediates generated with [bis(trifluoro-acetoxy)iodo]benzene (PIFA) and phenolic substrates.[66]



Scheme 53. Iodine(III)-mediated allylation of silyl enol ethers

In 2015, it was shown that, while the direct α-cyanation of ketones using iodosylbenzene in the presence of $BF_3 \cdot OEt_2$ and TMSCN was not feasible, utilizing the corresponding trimethyl silyl enol ethers led to the desired α-cyano ketones in poor to good yields (Scheme 54a).[67] The synthetic utility of the products obtained was demonstrated by the synthesis of potentially N-O and N-N containing heterocycles (Scheme 54b).



Scheme 54. a) Cyanation of silyl enol ethers. b) Heterocycles syntheses

Very recently, Wirth and co-worker have reported the oxidative coupling of bis(silyl enol ethers) promoted by activated PIDA.[68] The method allows for the construction of the 1,4-dicarbonyl compounds in good to very good yields (Scheme 55).

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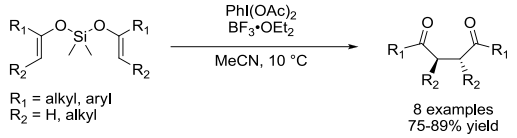
[66] S. Quideau, M. A. Looney, L. Pouységu, Org. Lett. **1999**, 1, 1651–1654.

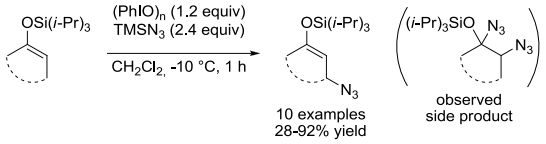
[67] H. Shen, J. Li, Q. Liu, J. Pan, R. Huang, Y. Xiong, J. Org. Chem. **2015**, 80, 7212–7218.

[68] P. Mizar, T. Wirth, Angew. Chem. Int. Ed. **2014**, 53, 5993–5997.



Scheme 55. Iodine(III)-mediated coupling of bis(silyl enol ethers)

In analogy to the work reported in section 3.1, the development of iodine(III)-mediated C-N bond formation on silyl enol ethers have initially revolved around azidation chemistry. In 1992 Magnus *et al.* have reported the β-azido functionalization of trisisopropylsilyl enol ethers (Scheme 56).[47] The establishment of scope of the reaction was mainly done with cyclic enol ethers. Interestingly, depending on the order of addition of the reagents to generate the active iodine(III) species, the diazidation reaction was found to be competing with the allylic azidation pathway.



Scheme 56. β-azidation of silyl enol ethers

Immediately following their first report on the development of this methodology, they reported synthetic applications of the β-azido functionalized enol ethers by replacing the azido group with other nucleophiles.[69] They also demonstrated that the β-azido enol ethers could be directly converted to the corresponding enones by the action of TBAF.[70] They reinvestigated the factors governing the formation of the β-azidation versus the *bis*-α-azidation products and found the reaction temperature to be the most influencial one. They also discovered that the addition of catalytic quantity of TEMPO could significantly enhance the formation of the *bis*-azidation product (Scheme 57).[71] Two extensive full papers were published to describe the scope and synthetic applications of these methodologies.[72,73]

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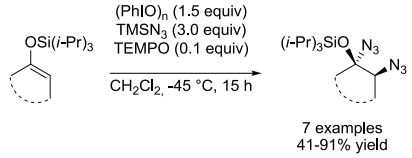
[69] P. Magnus, J. Lacour, J. Am. Chem. Soc. **1992**, 114, 3993–3994.

[70] P. Magnus, A. Evans, J. Lacour, Tetrahedron Lett. **1992**, 33, 2933–2936.

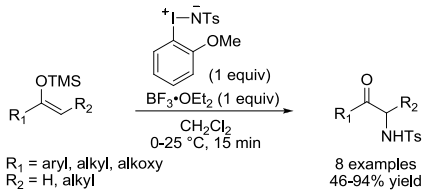
[71] P. Magnus, M. B. Roe, C. Hulme, J. Chem. Soc., Chem. Commun. **1995**, 263–265.

[72] P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, J. Am. Chem. Soc. **1996**, 118, 3406–3418.



Scheme 57. Bis-α-azidation of silyl enol ethers

The use of iminoiodanes as nitrene precursors in transition metal-catalyzed processes has been reported numerous times.[74] It is not covered in this review as the active species are considered to be nitrene-metal complexes. However, in 2011, Zhdankin, Nemykin and co-workers have demonstrated that the tosylamination of silyl enol ethers was feasible under metal-free conditions.[75] They enhanced the electrophilic character of an iminoiodane bearing an *ortho*-alkoxy group to the aryl group with $BF_3 \cdot OEt_2$. Under these conditions numerous silyl enol ethers were converted to their corresponding α-tosylamino ketones in low to excellent yields (Scheme 58). The *ortho*-alkoxy substituent on the aryl ring is key in obtaining the solubility and reactivity necessary for the reaction.



Scheme 58. Metal-free tosylamination of silyl enol ethers

Seminal work by Wirth and co-workers has been reported recently. They have developed a very interesting synthetic platform for the introduction of nucleophiles to ketones with (bisacetoxyiodo)-aryls reagents.[68] The reaction results in the transfer of a latent nucleophilic group on the silyl moiety of the starting silyl enol ethers (Scheme 59a). Of particular importance, the use of chiral iodine(III) reagents (Scheme 59b) is possible, enabling the direct formation of chiral non-racemic α-substituted ketones. The nature of the nucleophile can vary, opening a synthetic pathway for the stereoselective

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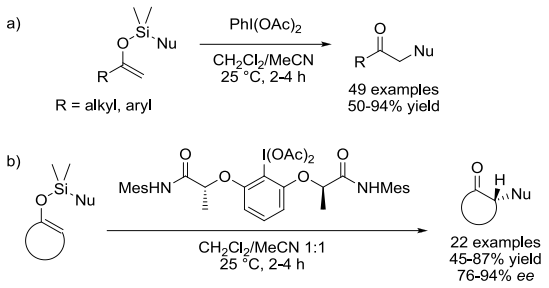
[73] P. Magnus, J. Lacour, P. A. Evans, P. Rigollier, H. Tobler, J. Am. Chem. Soc. **1998**, 120, 12486–12499.

[74] D. A. Evans, M. T. Bilodeau, M. M. Faul, J. Am. Chem. Soc. **1994**, 116, 2742–2753.

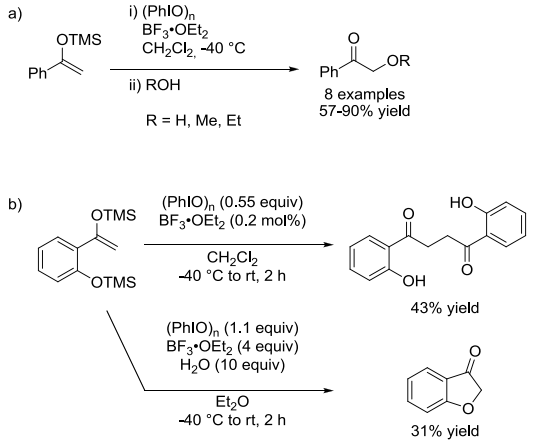
[75] A. Yoshimura, V. N. Nemykin, V. V. Zhdankin, Chem. - Eur. J. **2011**, 17, 10538–10541.

formation of C-C, C-O and C-N bond formation by means of iodine(III) oxidation. It is noteworthy that fully substituted silyl enol ethers could be employed and led to similar yields and enantiomeric excess, opening a route toward the synthesis of enantioenriched α,α-disubstituted cycloalkanones.



Scheme 59. Umpolung strategy developed by Wirth and co-worker

A wide variety of oxygen-based nucleophiles were used in iodine(III)-mediated transformations of silyl enol ethers. In their preliminary work to generate iodonium salts from enol ethers, Moriarty *et al.* have showed that the latter could be trapped by protic solvents to furnish the α-hydroxy or α-alkoxy ketones in fair to excellent yields (Scheme 60a).[59] A year later, they reported the intramolecular C-O bond formation between a silyl ether and a silyl enol ether (Scheme 60b).[76] Interestingly, the outcome of the reaction is changed by the presence of water.



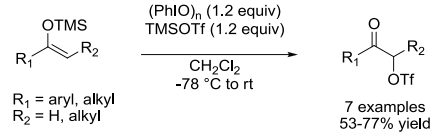
Scheme 60. Iodine(III)-mediated α-oxylation of silyl enol ethers

[76] R. M. Moriarty, O. Prakash, M. P. Duncan, Synth. Commun. **1986**, 16, 1239–1245.

They pursued their study of the reactivity of silyl enol ethers toward different iodine(III) reagents and, in 1989, reported that they could be cleanly converted to their corresponding α-sulfonyloxy ketones by reaction with [hydroxyl(sulfonyloxy)iodo]-benzene reagents (Scheme 61).[77]

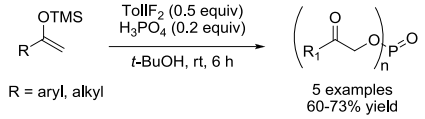
Scheme 61. Iodine(III)-mediated α-sulfonyloxylation of silyl enol ethers

The same year, they demonstrated that the addition of even weaker oxygen-based nucleophiles was possible with the synthesis of α-triflyloxy ketones from the corresponding silyl enol ethers (Scheme 62).[78]



Scheme 62. Iodine(III)-mediated α-trifyloxylation of silyl enol ethers

In 1994, Koser *et al.* reported the synthesis of tris-ketol phosphates from silyl enol ethers.[79] In this synthetic transformation, phosphoric acid acts as the nucleophile. The scope exploration was assessed only on mono-substituted silyl enol ethers (Scheme 63).



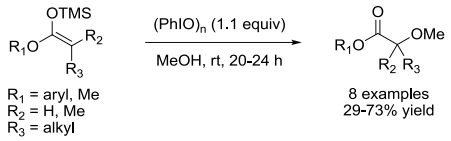
[77] R. M. Moriarty, R. Penmasta, A. K. Awasthi, W. R. Epa, I. Prakash, J. Org. Chem. **1989**, 54, 1101–1104.

[78] R. M. Moriarty, W. R. Epa, R. Penmasta, A. K. Awasthi, Tetrahedron Lett. **1989**, 30, 667 – 670.

[79] G. F. Koser, K. Chen, Y. Huang, C. A. Summers, J. Chem. Soc. Perkin Trans. 1 **1994**, 1375–1376.

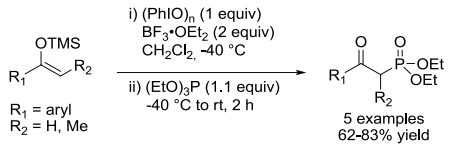
Scheme 63. Iodine(III)-mediated synthesis of tris-ketol phosphates

In 1997, Moriarty, Prakash, and co-workers reported the α-methoxylation of trimethylsilyl ketene acetals using iodosobenzene in dry methanol.[80] Interestingly, the activation of iodosobenzene with a Lewis acid was not necessary in this methodology (Scheme 64).



Scheme 64. Iodine(III)-mediated synthesis of α-methoxy esters and lactones

An iodine(III)-mediated C-P bond formation has been reported by Kim *et al.*[81] Using a protocol very similar to previous Moriarty's work, they have added the iodonium salt intermediates derived from silyl enol ethers to triethyl phosphite, yielding the corresponding β-keto phosphonates in fair to very good yields (Scheme 65).



Scheme 65. Iodine(III)-mediated synthesis of β-keto phosphonates

Moriarty, Prakash and co-workers have evaluated the extent of their methodology by attempting oxidative C-S bond formation. In a process that is hypothesized to be analogous to that of α-tosyloxylation of the same substrates, the α-thiocyanation of ketene silyl acetals and silyl enol ethers is done to afford α-thiocyano ketones and esters (Scheme 66).[82] The active oxidative reagent, $PhI(SCN)_2$, was formed *in situ* by reaction of $PhICl_2$ with $Pb(SCN)_2$. In a subsequent full paper, they have extended

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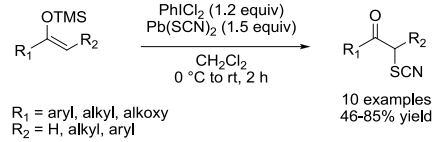
[80] R. M. Moriarty, N. Rani, C. Condeiu, M. P. Duncan, O. Prakash, Synth. Commun. **1997**, 27, 3273–3277.

[81] D. Young Kim, J. Yang Mang, D. Young Oh, Synth. Commun. **1994**, 24, 629–634.

[82] O. Prakash, N. Rani, V. Sharma, R. M. Moriarty, Synlett **1997**, 1997, 1255–1256.

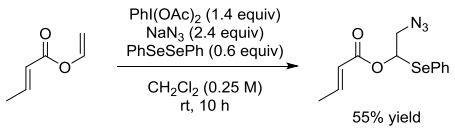
the scope investigation to β-dicarbonyl compounds and 2-trimethylsilyloxy furane toward oxidative thiocyanation.[83]



Scheme 66. Iodine(III)-mediated synthesis of α-thiocyanation of ketene silyl acetals and silyl enol ethers

3.2. Enol esters (8, 9)

Probably due to their expected lower reactivity, the investigation of enol esters in iodine(III)-mediated processes has been scarce. In their 1991 study, Tingoli *et al.* have reported one example of a reaction with an enol ester to demonstrate the electronic properties effect of the latter (Scheme 67).[43]

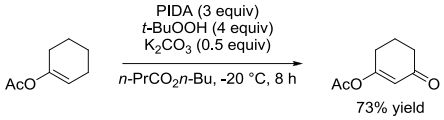


Scheme 67. Azido-phenylselenylation of an enol ester

In 2010, Yeung and co-worker have developed an allylic oxidation method involving PIDA and *t*-butylhydroperoxide.[84] They reported one successful example of allylic oxidation of an enol ester (Scheme 68). One must note that the proposed mechanism involves abstraction of the allylic hydrogen by *t*-butylperoxy radical and no direct reaction with the enol ester. The method works with a variety of vinylic substrates.

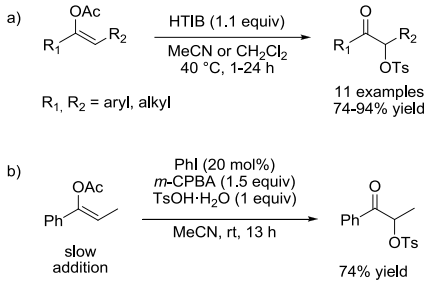
[83] O. Prakash, H. Kaur, H. Batra, N. Rani, S. P. Singh, R. M. Moriarty, J. Org. Chem. **2001**, 66, 2019–2023.

[84] Y. Zhao, Y.-Y. Yeung, Org. Lett. **2010**, 12, 2128–2131



Scheme 68. Iodine(III)-mediated allylic oxidation

Our group has recently become interested in enol esters substrates for hypervalent iodine chemistry. The catalytic enantioselective α-tosyloxylation of ketones is a promising reaction, but is plagued by low enantioselectivities. In an effort to solve this longstanding problem, our group has developed numerous new catalysts to promote this reaction.[85]More recently, we have published a computational study that raised questions on the feasibility to attain high selectivities from ketone substrates.[86] In this context, we have investigated numerous enol surrogates and reported recently the clean conversion of enol esters to their corresponding α-tosyloxy ketone products in high yields.[87] These substrates have the marked advantage that they can be converted under both stoichiometric and catalytic conditions (Scheme 69). Sulfonyl esters can also be used as substrates, but they possess reduced reactivity.



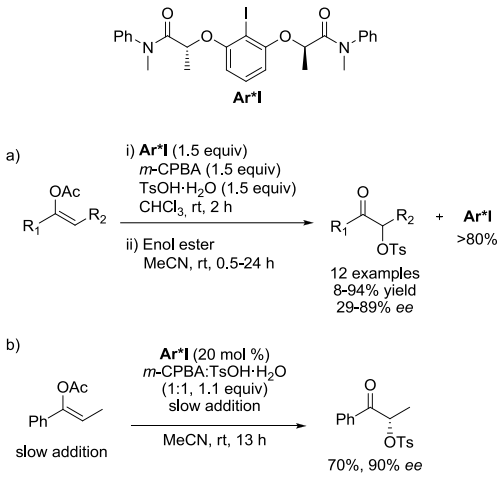
Scheme 69. a) Iodine(III)-mediated synthesis of a-tosyloxy ketones from enol esters. b) Catalytic conditions to promote the conversion of enol esters

[85] (a) M.-È. Thérien, A.-A. Guilbault, C. Y. Legault, Tetrahedron: Asymmetry **2013**, 24, 1193–1197; (b) A.-A. Guilbault, C. Y. Legault, ACS Catal. **2012**, 2, 219–222; (c) A.-A. Guilbault, B. Basdevant, V. Wanie, C. Y. Legault, J. Org. Chem. **2012**, 77, 11283–11295.

[86] S. Beaulieu, C. Y. Legault, Chem. - Eur. J. **2015**, 21, 11206–11211.

[87] B. Basdevant, C. Y. Legault, J. Org. Chem. **2015**, 80, 6897–6902.

Following these promising results, stoichiometric and catalytic enantioselective conditions were developed to convert acetyl enol esters to their corresponding chiral non-racemic α-tosyloxy ketones.[88] This development enabled our group to obtain these useful chiral building blocks with unprecedented levels of enantioselectivities (Scheme 70). These results provide strong support to the previously published computational study.



Scheme 70. a) Enantioselective Iodine(III)-mediated synthesis of a-tosyloxy ketones from enol esters b) Catalytic enantioselective conditions to promote the conversion of enol esters

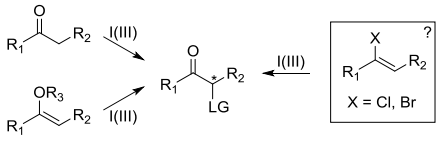
4. Halide-substituted Substrates

Few unsaturated organic halides have been showcased as substrates in hypervalent iodine reagent-mediated oxidative rearrangements. They can be categorized in two categories: vinyl halides (**10**) and alkynyl halides (**11**).

4.1. Vinyl halides (10)

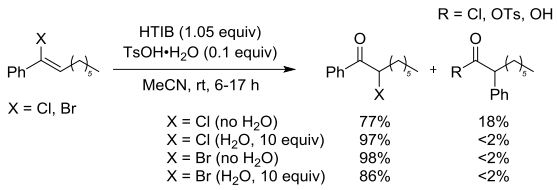
As described in section 3.2, our group became interested in the use of enol analogs, such as acyl and sulfonyl enol esters. In this context, our interest in the reactivity of isolable enol derivatives led to the investigation of the vinyl halides family. It was hypothesized that such alkenes, with the same oxidation level and somewhat similar π-donating and σ-attracting properties of enols, could exhibit a reactivity similar to enols in iodine(III) chemistry (Scheme 71).

[88] B. Basdevant, C. Y. Legault, Org. Lett. **2015**, 17, 4918–4921.



Scheme 71. Rational behind the use of vinyl halides as enol surrogates

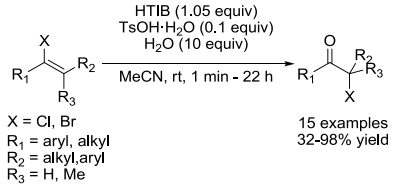
We thus investigated the reactivity of these substrates toward HTIB.[89] They were found to react very cleanly and afford, contrary to acyl enol esters, the corresponding α-halo ketones instead of the α-tosyloxy ketones (Scheme 72). It is interesting to note that some aryl migration product was observed with the vinyl chloride substrate. Addition of water to the reaction mixture prevented this side reaction of occurring. The vinyl bromide substrate did not suffer from this 1,2-internal phenyl migration and the α-bromo ketone could be obtained almost quantitatively without the addition of water.



Scheme 72. Iodine(III)-mediated oxidative hydrolysis of vinyl halides

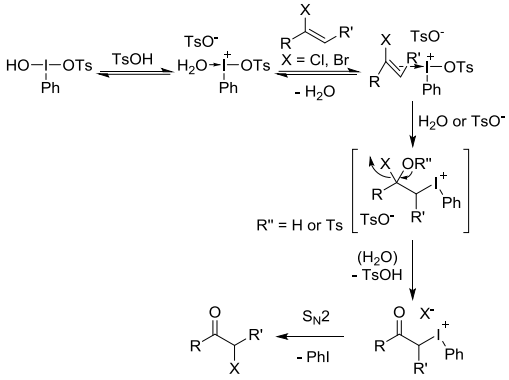
The methodology was found to support a variety of substrates. This preliminary investigation focused mostly on styrene derivatives. It is noteworthy that even tetrasubstituted alkenes react to afford ketones bearing a quaternary α-halo center. An aliphatic substrate, bromocycloheptene, showed a different reactivity profile and led to the formation of the desired α-bromo ketone in only low (32%) yield. Examples in the scope show that the reaction rate is slowed by deactivated and strained alkenes and notably augmented by activated alkenes (Scheme 73).

[89] A. Jobin-Des Lauriers, C. Y. Legault, Org. Lett. **2016**, 18, 108–111



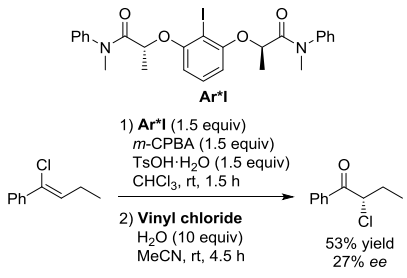
Scheme 73. Scope of the reaction

As described in Scheme 72, small amount of the phenyl 1,2-migration product was isolated, raising the possibility that the halogen could also transfer internally. A scrambling experiment was done and demonstrated that it was not, at least in part, the case. From these results, the currently proposed mechanism involves a release and catch process (Scheme 74).



Scheme 74. Proposed mechanism

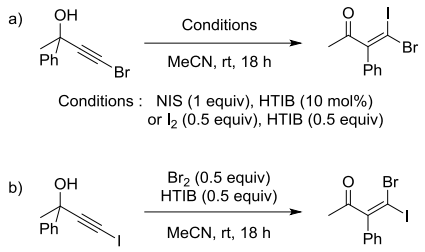
Attempt to render the process enantioselective was done, with some success, making it the first synthetic transformation to directly convert a prochiral vinyl halide to a chiral non-racemic α-halo ketone (Scheme 75).



Scheme 75. Enantioselective variant

4.2. Alkynyl halides (11)

Fully substituted α-hydroxy haloalkynes have been exploited for oxidation-induced type rearrangements for the first time in the ’90. Mc Nelis and co-workers have published numerous articles demonstrating the feasibility of this reaction on various substrates. It consists of a semi-pinacolic rearrangement of secondary and tertiary 3-bromoprop-2-ynol and 3-iodoprop-2-ynol by reacting with HTIB and an oxidant in acetonitrile at room temperature. Through the oxidation of the triple bond activated by the formation of an iodonium bridge, the richest substituent migrates to yield fully substituted acroleins and enones.[90] In the case of the oxidation of 3-bromopro-2-ynol with NIS, HTIB simply acts as an acid, as the reaction can proceed under simple acid (*p*-TsOH) catalysis (Scheme 76a). The reaction of 3-iodoprop-2-ynol requires however a 1:1 mixture of bromine and HTIB to proceed (Scheme 76b). They published later that year an evaluation of the reaction conditions on the yields obtained.[91]



Scheme 76. Semi-pinacolic methodology developed Mc Nelis and co-workers

They applied their methodology to ring expansion chemistry, on cyclopentanol (Scheme 77a),[92] camphor (Scheme 77b),[93] fluorenol (Scheme 77c),[94] and adamantol (Scheme 77d)[95] derivatives. A full paper was published a year later to expand on this work.[96] In 1996, they reinvestigated the stereoelectronic effect involved in the rearrangement of cyclopentanol derivatives.[97]

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[90] G. J. Angara, P. Bovonsombat, E. McNeils, Tetrahedron Lett. **1992**, 33, 2285–2288.

[91] P. Bovonsombat, E. McNelis, Tetrahedron Lett. **1992**, 33, 7705–7708.

[92] P. Bovonsombat, E. McNelis, Tetrahedron **1993**, 49, 1525–1534.

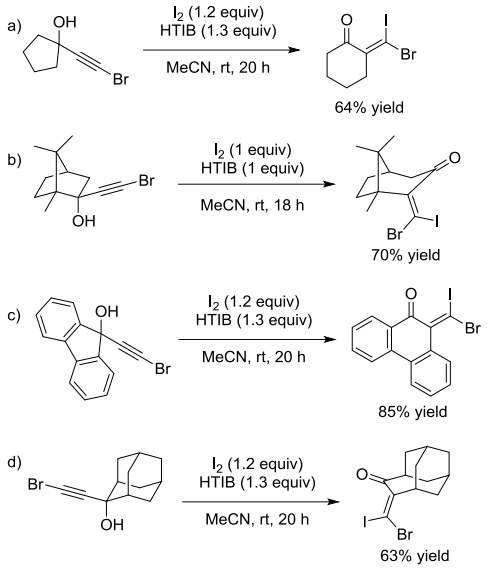
[93] P. Bovonsombat, E. McNelis, Tetrahedron Lett. **1993**, 34, 4277–4280.

[94] P. Bovonsombat, E. Mc Nelis, Tetrahedron Lett. **1994**, 35, 6431–6432.

[95] P. Bovonsombat, E. Mc Nelis, Synth. Commun. **1995**, 25, 1223–1229.

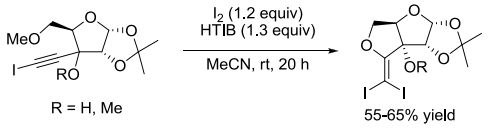
[96] E. Djuardi, P. Bovonsombat, E. M. Nelis, Tetrahedron **1994**, 50, 11793–11802.

[97] X. Herault, E. Mc Nelis, Tetrahedron **1996**, 52, 10267–10278.



Scheme 77. Ring expansion methodology developed Mc Nelis and co-workers

Lastly, they showed on a substrate derived from xylose that a nearby protected alcohol on a substrate could prevent the ring expansion to occur (Scheme 78).[98]



Scheme 78. Interrupted ring expansion

5. Conclusions

From the diversity of available substrates and the wide assortment of possible mechanistic pathways, iodine(III)-mediated synthetic transformations with enol and ynol surrogates have contributed greatly to the field of hypervalent iodine chemistry. As described, they have played, in some cases, a vital role to solve current limitations involving ketone substrates. They furnished the levels of reactivity and selectivity necessary to achieve synthetic utility. Additionally, for some of the families displayed, their investigation is still preliminary and numerous new synthetically useful methodologies could be developed in the near future.

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[98] E. Djuardi, E. Mc Nelis, Tetrahedron Lett. **1999**, 40, 7193–7196.

CHAPITRE 2: IODINE(III)-MEDIATED OXIDATIVE HYDROLYSIS OF HALOALKENES: ACCESS TO A-HALO KETONES BY A RELEASE-AND-CATCH MECHANISM

2.1. Transposition oxydante d'haloalcènes en α-halo cétones.

Tel que décrit dans la revue de littérature de la section précédente, la réaction en question a été l'objet principal du projet de maîtrise et constitue une autre contribution du groupe dans la recherche sur la réactivité d'analogues d'énol vis-à-vis de λ^3-iodanes. Alors que mes prédécesseurs se sont particulièrement intéressés aux acétates d'énol, l'article présenté traite de la réactivité d'haloalcènes, des alcènes conjugués de mêmes degrés d'oxydation. Ma participation a consisté en la rédaction du premier jet, à mener les expériences et analyses chimiques ainsi qu'à une participation active au reste de la rédaction.

2.2. Article

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Org. Lett., **2016**, *18* (1), pp 108–111.

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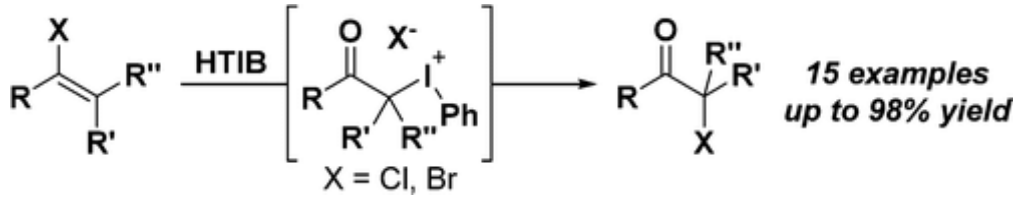
Publication Date (Web): December 17, 2015

ABSTRACT:



An unprecedented iodine(III)-mediated oxidative transposition of vinyl halides has been accomplished. The products obtained, α-halo ketones, are useful and polyvalent synthetic precursors. There are only a handful of reported examples of the direct conversion of vinyl halides to their corresponding α-halo carbonyl compounds. Insights on the mechanism and demonstration that this synthetic transformation can be done under enantioselective conditions are reported.

Although hypervalent iodine reagents have been known for over a century, they have recently become a subject of growing and keen interest in the field of chemistry.[1] On top of being mild, selective, eco-friendly, and versatile oxidants, iodine(III) and iodine(V) reagents have also proven their utility in performing synthetically relevant transformations, such as phenolic dearomatizations[2] and various other

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[1] (a) Zhdankin, V. V. *Hypervalent iodine chemistry: preparation, structure, and synthetic applications of polyvalent iodine compounds*, Wiley, Chichester, UK, **2013**. (b) Tohma, H.; Kita Y. in *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer: Berlin, **2003**, p 209. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327. (e) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis* Academic Press, San Diego, **1997**.

[2] (a) Bosset, C.; Coffinier, R.; Peixoto, P. A.; El Assal, M.; Miqueu, K.; Sotiropoulos, J.-M.; Pouységu, L.; Quideau, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 9860. (b) Volp, K.; Harned, A. M. *Chem. Commun.* **2013**, *49*, 3001. (c) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 9215. (d) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (e) Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841. (f) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4605. (g) Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1221. (h) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787.

oxidative rearrangements.[3] They can also act as safer alternatives to some, toxic metal-based oxidants, such as thallium.[4] Lately, there have been numerous efforts in the development of stereoselective methods involving these reagents.[5]

The iodine(III)-mediated synthesis of functionalized ketone derivatives has been a particularly active area of research.[6] This is not surprising considering the ubiquitous nature of α-functionalized ketones in natural and synthetic compounds. One particularly useful approach exploits iodine(III) chemistry to introduce by oxidation a leaving group at the α position of the carbonyl (Scheme 79a). If performed under enantioselective conditions, the resulting products are versatile chiral precursors for stereoselective synthesis. In this context, our group has been interested in the synthesis of chiral non-racemic α-tosyloxy ketone derivatives. For more than 15 years, the published methods involved the direct α-tosyloxylation of ketones.[7] Recently, we have raised the issue that the probable mechanism

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[3] (a) Singh, F. V.; Wirth, T. *Chem. Asian J.* **2014**, *9*, 950. (b) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (c) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086. (d) Zhdankin, V. V. *Arkivoc* **2009**, *1*, 1. (e) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402. (f) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

[4] Khanna, M. S.; Garg, C. P.; Kapoor, R. P. *Tetrahedron Lett.* **1992**, *33*, 1495. Iodine(III) variant: Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487.

[5] Reviews on hypervalent iodine-mediated asymmetric transformations: (a) Kumar, R.; Wirth. T. *Top. Curr. Chem.* **2015** (doi: 10.1007/128_2015_639). (b) Berthiol, F. *Synthesis* **2015**, *47*, 587. (c) Parra, A.; Reboredo, S. *Chem. Eur. J.* **2013**, *19*, 17244. (d) Ngatimin, M.; Lupton, D. W. *Aust. J. Chem.* **2010**, *63*, 653.

[6] Reviews on hypervalent iodine-mediated functionalization of carbonyl compounds: (a) Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C. *Org. Biomol. Chem.* **2014**, *12*, 4278. (b) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517.

[7] (a) Brenet, S.; Minozzi, C.; Clarens, B.; Amiri, L.; Berthiol, F. *Synthesis* **2015**, *47*, 3859. (b) Brenet, S.; Berthiol, F.; Einhorn, J. *Eur. J. Org. Chem.* **2013**, 8094. (c) Thérien, M.-È.; Guilbault, A.-A.; Legault, C. Y. *Tetrahedron: Asymmetry* **2013**, *24*, 1193. (d) Guilbault, A.-A.; Basdevant, B.; Wanie, V.; Legault, C. Y. *J. Org. Chem.* **2012**, *77*, 11283. (e) Guilbault, A.-A.; Legault, C. Y. *ACS Catalysis* **2012**, *2*, 219. (f) Rodriguez, A.; Moran, W. J. *Synthesis* **2012**, *44*, 1178. (g) Yu, J.; Cui, J.; Hou, X.-S.; Liu, S.-S.; Gao, W.-C.; Jiang, S.; Tian, J.; Zhang, C. *Tetrahedron: Asymmetry* **2011**, *22*, 2039. (h) Farooq, U.;

involved for the direct α-tosyloxylation of ketones could prevent achievement of high selectivities.[8] In an effort to solve this issue, we have developed reaction conditions that have given access to the desired α-tosyloxy ketones from their corresponding enol esters (Scheme 79b, R'' = Ac), with unprecedented levels of enantioselectivities (up to 90% *ee*).[9]

We envisioned that other vinylic substrates having the same oxidation state as enol derivatives, such as vinyl halides, could thus serve as α-substituted ketone precursors (Scheme 79c). Only scarce examples are found in the literature for the direct conversion of vinyl halides to their corresponding α-halo ketone derivatives.[10] In analogy to α-tosyloxy ketones, the α-halo ketones families have the same versality and are common and useful building blocks in synthetic chemistry.[11]

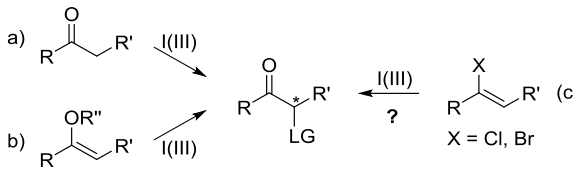
Schäfer, S.; Shah, A. A.; Freudendahl, D. M.; Wirth, T. *Synthesis* **2010**, 1023. (i) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315. (j) Richardson, R. D.; Page, T. K.; Altermann, S. M.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538. (k) Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T. *Eur. J. Org. Chem.* **2001**, 1569. (l) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674. (m) Wirth, T.; Hirt, U. H. *Tetrahedron: Asymmetry* **1997**, *8*, 23.

[8] Beaulieu S.; Legault, C. Y. *Chem. Eur. J.* **2015**, *21*, 11206.

[9] Basdevant, B.; Legault, C. Y. *Org. Lett.* **2015**, *17*, 4918.

[10] (a) Gonzalez-de-Castro, A.; Xiao, J. *J. Am. Chem. Soc.* **2015**, *137*, 8206. (b) VanBrunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003**, *68*, 3323. (c) Huang, B.; Gupton, J. T.; Hansen, K. C.; Idoux, J. P. *Synth. Commun.* **1996**, *26*, 165. (d) Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485. (e) Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993**, *34*, 4481. (f) Duncan, R.; Drueckhammer, D. G. *Tetrahedron Lett.* **1993**, *34*, 1733. (g) Hsiao, C.-N.; Leanna, M. R.; Bhagavatula, L.; DeLara, E.; Zydowski, T. M.; Morton, H. E. *Synth. Commun.* **1990**, *20*, 3507.

[11] De Kimpe, N.; Verhe, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Halolmines*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, **1988**, p.496.



Scheme 79. Concept of the described research

Accessing these products from the vinyl halides family is particularly interesting in this regard, due the numerous synthetic methods to access them from non-ketonic precursors.[12] We report herein the oxidation of vinyl halides to their corresponding α-halo ketones in high yields and mild conditions. To evaluate the reactivity of the described compound family, we elected to use vinyl halides **1a** and **1b**, derived from octanophenone, for the low volatilities of the substrates and final products. For the sake of simplicity, these substrates were obtained directly from the ketone.[13] The results of the optimization are described in Table 1. The reaction of **1a** with [hydroxy(tosyloxy)iodo]benzene (HTIB) did not result in the formation of the α-tosyloxy ketone product, but instead its chloro analog (**2a**). The formation of acid derivatives **3** in small amounts was observed as a consequence of 1,2-aryl migration. Isolated yields of **3** compounds could not be obtained due to their partial and continuous hydrolysis over the course of the purification by flash chromatography on silica gel.

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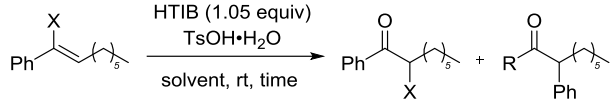
[12] (a) Trost, B. M.; Pinkerton, A. B. *Tetrahedron Lett.* **2000**, *41*, 9627. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965. (c) Roush, W. R.; Moriarty, K. J; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.

[13] See the Supporting Information for details.

Table 1. Conditions Screening[a]



1a (X = Cl)
1b (X = Br)

2a (X = Cl)
2b (X = Br)

3
R = OTs, Cl, OH

entry	*TsOH (equiv)*	*solvent*	*time (h)*	***2*[%][b]**	***3* [%][c]**
1	0	MeCN	20	69	15
2	0.1	MeCN	5	77	18
3	0.5	MeCN	2	79	21
4	1	MeCN	1.5	80	20
5	0.1	MeCN[d]	6	97	<2
6	0.1	MeCN/H_2O(1:1)	24	76	<2
7	0.1	H_2O	72	29	<2
8	0.1	CH_2Cl_2	48	68	20
9	0.1	CH_2Cl_2[d]	26	70	30
10	0.1	EtOAc	72	46	<2
11	0.1	THF	1	53	<2
12[e]	0.1	MeCN[d]	17	86	<2
13[e]	0.1	MeCN	17	98	<2

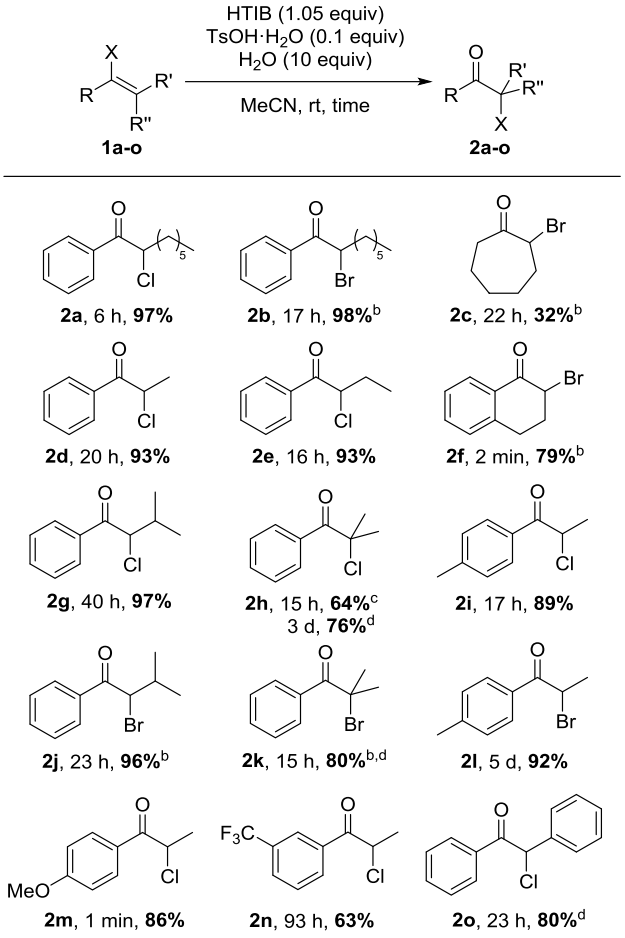
[a] Unless otherwise stated, **1a** was used; [b] Isolated yield; [c] Yield determined by ^{1}H NMR of the crude mixture, with respect to isolated **2**; [d] 10 equiv of water was added to the reaction; [e] Reaction performed with **1b**.

The effect of adding TsOH•H_2O in increasing amounts was studied to determine if this additive could accelerate the reaction rate, as it was previously observed for the reaction of HTIB with enol esters.[14] It was found to furnish a great acceleration effect, while not affecting the relative **2a**/**3** formation ratio (entries 2-4). Since the concentration of TsOH increases as HTIB is reduced during the reaction process, a sub-stoichiometric loading (0.1 equiv) of TsOH is sufficient to achieve noticeable overall acceleration, and was used for the remainder of the optimization. As hydrolysis is most probably involved in the reaction process, the effect of water was next evaluated. Addition of 10 equivalents of water resulted in no acceleration, but in a very clean conversion of **1a** to **2a**, with no detectable aryl migration products **3** (entry 5). Attempts to perform the reaction in either equivolumic MeCN/water solution or directly in water resulted in lower yields of **2a**, but no observable formation of phenyl migration products (entries 6-7). Other solvents (entries 8-11) were tested, but only resulted in lower

[14] Basdevant, B.; Legault, C. Y. *J. Org. Chem.* **2015**, *80*, 6897.

yields and side products formation. The addition of 10 equivalents of water in dichloromethane did not prevent the formation of migration products **3**. The optimized conditions were evaluated on vinyl bromide **1b**; a lower yield and no migration products were observed (entry 12). Presence of the α-hydroxy ketone in the crude mixture suggested susceptibility of **2b** toward hydrolysis. The reaction was thus performed without the addition of water; the α-bromo product **2b** was obtained in essentially quantitative yield, with no noticeable migration products (entry 13).

With these optimized conditions in hand, the scope of this new transformation was investigated with various vinyl chlorides and bromides. The results are summarized in Scheme 80. The transformation is efficient on styrene analogs (R = aromatic), with excellent yields in most cases. It is important to point out that it does however proceed with some success on fully aliphatic substituted vinyl bromide **1c**, affording product **2c** with 32% yield. Conversion of **1c** was complete, with the formation of numerous unidentified side products.



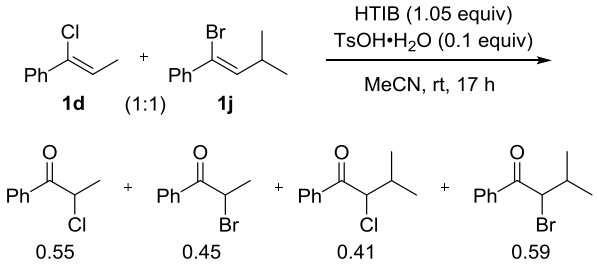
Scheme 80. Reaction Scope[a]

[a] Isolated yields reported; [b] No water was added in the reaction; [c] Reaction performed at 55 °C; [d] Reaction performed at 40 °C.

The method supports variation on the other portion of the styrene derivatives (R', R''). For example, vinyl chloride and bromide **1g** and **1j**, respectively, were converted in almost quantitative yields to their respective α-halo ketone products. The reaction can even proceed on tetrasubstituted vinyl halides (**1h** and **1k**), although higher reaction temperatures (40-55 °C) are required to obtain complete conversion. Cyclic vinyl bromide **1f** afforded the desired product **2f** in a very fast reaction. In the last three cases, the lower yield is attributed to partial formation of the enone products. These results are in stark contrast with the behavior observed for the corresponding enol ester analogs, which afforded mainly the formation of the corresponding enones in low yield.[13,14] The electronic properties of the aromatic group of the styrene derivatives greatly affect the reactivity. Vinyl halide **1m**, bearing a *p*-methoxy

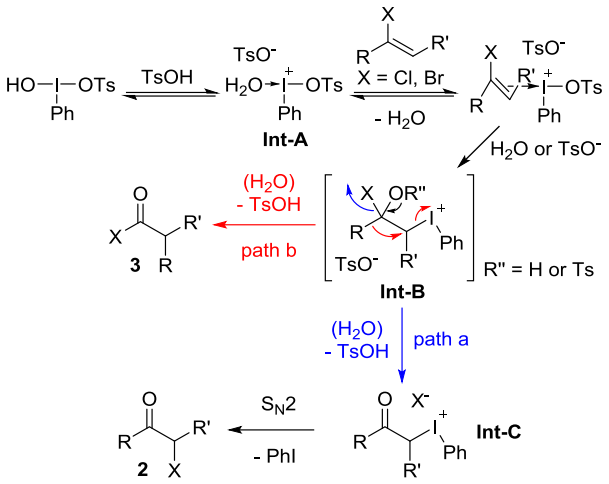
phenyl group, is converted almost instantly to product **2m**. The lower yield is attributed to numerous unidentified side products, but aryl migration products **3** are observed in higher quantities in the crude mixture. In contrast, almost 4 days of reaction is required to achieve complete conversion of substrate **1n**, bearing a *m*-trifluoromethyl phenyl group. The described methodology demonstrates a larger scope than the known methods to directly convert vinyl halides to α-halo ketones.

During the optimization process, the observation of the aryl migration products **3** prompted the investigation of the reaction mechanism. These products point toward a potential internal transposition of the halogen atom in the reaction process. To assess the feasibility of the latter *versus* an external halide attack manifold, a scrambling experiment was performed. An equimolar mixture of substrates **1d** and **1j** was subjected to the optimized reaction conditions. The outcome is presented in Scheme 81.



Scheme 81. Scrambling experiment

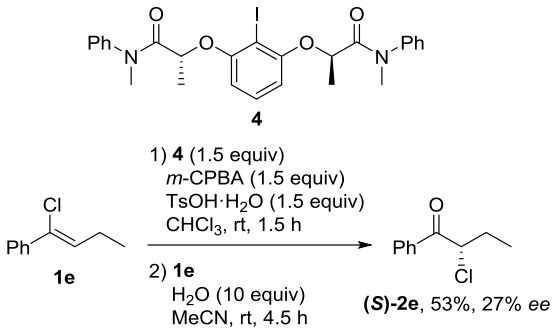
Starting from an equimolar mixture of vinyl halides **1d** and **1j**, the four possible α-halo ketones products were observed in almost equimolar quantities. The slight variance in ratio could either be explained by the different rates of conversion of **1d** and **1j**, or competing mechanisms. It is clear however that the main reaction pathway does not consist in an internal halide migration, but an external halide attack. Addition of 10 equivalents of water did not change noticeably the scrambling outcome. The possibility of the formation of the α-tosyloxy ketone product and subsequent S_N2 by an halide was infirmed; displacement reaction with HCl in similar reaction conditions was found to be very slow (35% conversion in 36 hours) in a control experiment.13 Additionally, the α-tosyloxy ketone products were not observed in the crude reaction mixtures, even if the reactions were stopped prior to completion. With these experimental clues in hand, we propose at the moment the mechanism illustrated in Scheme 82.



Scheme 82. Proposed mechanism

As observed for enol esters, the acceleration in the presence of TsOH is attributed to the formation of the phenyl tosyloxy iodonium intermediate **Int-A**, which is suggested to be the reactive iodine(III) species. Association of the vinyl halide and attack of a nucleophile (TsO^- or H_2O) lead to the formation of intermediate iodonium **Int-B**. At this point, depending on the rate of halide expulsion and migratory aptitude of the R group, there can be competing internal aryl migration through a semi-pinacolic displacement of PhI. In the case of vinyl chloride substrates, addition of water is necessary to accelerate expulsion of the chloride anion, through better solvation, and prevent formation of products **3**. In the case of vinyl bromides, the bromide anion is a better leaving group, and the competing aryl migration is not observed. No α-tosyloxy ketone is observed as the conjugate base of the strongest acid (HCl and HBr vs TsOH) will be the counterion of the iodonium intermediate **Int-C** and lead, by S_N2 substitution, to the final product. We coined this pathway a "release-and-catch" mechanism.

This unusual mechanism would have strong implications on the stereochemical aspects of this reaction. We thus tested preliminary enantioselective conditions to determine if this transformation would only furnish racemic products. The result is illustrated in Scheme 83.



Scheme 83. Enantioselective conditions

While the enantioselectivity observed is modest, the fact that the product is not racemic is very promising for the development of an enantioselective variant of this new transformation. The sense of induction was found to be the same obtained with enol esters using chiral iodoarene **4** suggesting a similar reaction process9. To the best of our knowledge, this is the first example of an enantioselective conversion of a prochiral vinyl halide to a corresponding chiral non-racemic α-halo ketone. In summary, this new iodine(III)-mediated transformation shows high potential to serve as a very useful synthetic tool. This methodology will be of great interest for the synthetic community considering the variety of methods to synthesize vinyl halides and the utility of α-halo ketone derivatives. The results described herein also raise numerous interesting questions for the field of hypervalent iodine chemistry. It is clear from the control experiments and the results obtained under enantioselective conditions that several aspects of the mechanism will need to be investigated in order to fully exploit this highly promising process. Joint computational/experimental investigations are currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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CONCLUSION GÉNÉRALE

L'étude de la réactivité des haloalcènes en tant qu'analogues d'énols vis-à-vis de réactifs d'iode hypervalent a constitué l'essentiel de la contribution scientifique lors du projet de maîtrise. La nouvelle transformation permettant l'obtention de cétones α-halogénées a été partagée avec la communauté scientifique. Aussi, une revue de la littérature de tous les précédents en matière de réactivités de substituts d'énols et d'ynols a constitué une contribution très intéressante pour les groupes de recherche en chimie, particulièrement ceux qui s'intéressent à l'iode hypervalent.

Pour commencer, les travaux publiés de Benoit Basdevant ont apporté une explication et une solution au problème d'α-tosyloxylation stéréosélective de cétones en utilisant des analogues d'énols stables. Les précedents en chimie ainsi que les évidences soulevées par les résultats de Benoit ont menés aux essais sur les haloalcènes. Ceux-ci ont été transformés en α-halocétones par un mécanisme plausible de relâche et capture, tel que suggéré par les études mécanistiques en laboratoire. Les conditions de la réaction ont été optimisées jusqu'à l'obtention de bons rendements pour divers substrats. Des efforts vers le développement de conditions stéréosélectives ont mené au premier exemple à ce jour où une alpha-chloro cétone est obtenue à partir d'un haloalcène prochiral, et ce, de façon énantioenrichie (27 % *ee*).

Des études computationnelles ont été menées en parallèle avec les expériences au laboratoire, par Odile Montounet[15]. Les résultats permettront de mieux cerner le mécanisme de la réaction et de corréler les données expérimentales, tels les proportions de produits de migration et de produit désiré. Les suites du projet sont maintenant menées par Robin Dagenais.

[15] Moutounet, O. La chimie computationnelle appliquée à l'étude de la réactivité et de la sélectivité de mécanismes réactionnels en chimie organique. Ph.D. Thèse, Janvier 2018.

ANNEXE 1 : PARTIE EXPÉRIMENTALE

General :

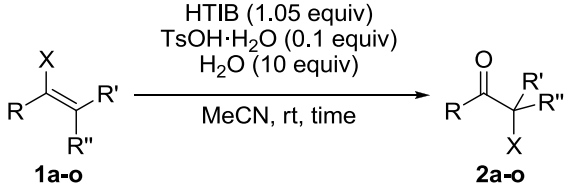
All non-aqueous reactions involving air or moisture sensitive compounds were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and glassware using standard techniques.[1] All glassware was stored in the oven and/or was flame dried prior to use under an inert atmosphere of gas. Anhydrous solvents were obtained either by distillation over sodium (THF, ether), over calcium hydride (CH_2Cl_2). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F_{254}). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine, or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) of the indicated solvent system according to standard technique.[2] Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra (^1H, ^{13}C, DEPT, COSY, HMQC) were recorded either on a Bruker Avance III HD 300 or Varian Mercury+ 400 spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextuplet, m = multiplet and br = broad), coupling constant in Hz, integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard. When ambiguous, proton and carbon assignments were established using COSY, NOESY, HMQC and DEPT experiments. High resolution mass spectra were performed at Université de Sherbrooke. Analytical High Performance Liquid Chromatography was performed on Shimadzu Prominence LC system equipped with diode array UV detector. Data are reported as follows: (column type, eluent, flow rate: retention time (t_r)).

Note 1: For all the acyclic vinyl halides, only the NMR signals for the major Z-isomer are reported.

*Note 2: Our attempts to obtain HRMS in Q-TOF for the vinyl halides **1c**, **1e**, **1g**, **1i**, **1j**, **1l**, **1m**, and **1n** were not successful. GC-MS (EI) were obtained instead for these compounds. The fragmentation patterns are consistent with the molecular formula. Furthermore, a recent report by Prati et al. has shown that for similar vinyl halides the GC-MS are always consistent with elemental analysis.[3]*

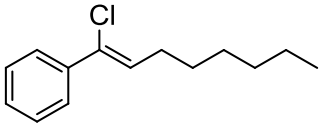
[1] D. F. Shriver, M. A. Drezdzon *The manipulation of air-sensitive compounds*; 2nd Edition; Wiley: New York, **1986**.
[2] W. C. Still, M. Kahn, A. Mitra *J. Org. Chem.* **1978**, *43*, 2923.
[3] Spaggiari, A; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, *72*, 2216.

General oxidative hydrolysis procedure



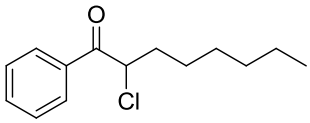
To a vial were added vinyl halide **1** (1 equiv.), MeCN (0.2 M), *p*-TsOH·H_2O (0.1 equiv.), H_2O* (10 equiv.) and HTIB (1.05 equiv.). The suspension was vigorously stirred at r.t. until a homogenous solution was obtained and let to stir at least an additional 30 minutes afterward. The solution was diluted with water (1:1) and extracted with three portions of Et_2O. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated by rotatory evaporation. The crude was purified by flash chromatography (0.5%-5% Et_2O in hexanes or pentane) to obtain the pure α-halo ketone **2**. * *Water was not added to reactions with vinyl bromides.*

***(Z)*-1-chloro-1-phenyl-octene.**[4]



The title compound was obtained from octanophenone (3.8 g, 18.82 mmol) following a literature procedure (see **(*Z*)-(1-Chloro-1-butenyl)benzene) (1e)**). 4.1g of the vinyl halide was isolated (99%) as a clear yellow oil; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.58-7.58 (m, 2H), 7.38-7.28 (m, 3H), 6.14 (t, J = 7.05 Hz, 1H), 2.38 (q, J = 7.17 Hz, 2H). 1.54-1.20 (m, 8H), 1.90 (t, J = 6.72 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.5, 132.8, 128.3, 128.2(2), 126.4, 31.9, 29.8, 29.2, 28.7, 22.8, 14.2.

2-chloro-1-phenyloctan-1-one (2a).

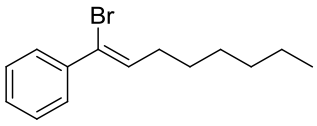


The title compound was obtained from **1a** (200.0 mg, 0.898 mmol) following the general oxidative hydrolysis procedure. 210.0 mg of the α-chloro ketone was obtained (98%) as a clear oil; R_f = 0.68

[4] Pratap, R.; Kazmaier, U. *Synlett* **2010**, *20*, 3073.

(10% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.03-7.99 (m, 2H), 7.64-7.57 (m, 1H), 7.53-7.47 (m, 2H), 5.11 (dd, *J* = 5.78 Hz, 8.10Hz, 1H), 2.19-1.94 (m, 2H), 1.60-1.23 (m, 8H), 0.88 (t, *J* = 6.89 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.9, 134.7, 133.9, 129.0, 128.9, 58.0, 33.8, 31.7, 28.9, 26.4, 22.7, 14.2; IR (neat) 2955, 2926, 2856, 1690 cm^{-1}. HRMS ESI-Q-TOF (m/z) calcd for $C_{14}H_{19}ClONa$ $[MNa]^+$ 261.1017, $C_{14}H_{20}ClO$ $[MH]^+$ 239.1203, found 261.1018, 239.1199.

(*Z*)-1-bromo-1-phenyloctene (1b).[5]

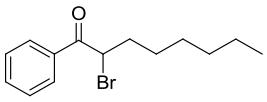


Acetyl bromide (1.8 mL, 23.8 mmol) was added to a solution of octanophenone (609.4 mg, 2.98 mmol) dissolved in anhydrous 1,2-DCE (3 mL, 1M). While the solution was vigorously stirred, $ZnBr_2/SiO_2$* (3 g, 2.22 mmol) was slowly added. After one hour, the solution was filtered. The filter cake was washed with pentane. The diluted solution was washed with three portions of saturated sodium bicarbonate or until CO_2 bubbling was no longer observed. The organic phase was dried over magnesium sulfate, filtered and concentrated by rotatory evaporation. The crude was purified by flash chromatography (0-0.5% EtOAc in hexanes). 606.5 mg of the vinyl halide was isolated (91%) as a clear oil; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.54-7.50 (m, 2H), 7.36-7.28 (m, 3H), 6.21 (s, 1H), 2.37 (dd, *J* = 7.06, 14.55 Hz, 2H), 1.56-1.26 (m, 8H), 0.93-0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 148.3, 132.1, 128.3 (2C), 127.7, 125.3, 32.7, 31.8, 29.1, 28.6, 22.8, 14.2.

*Silica gel supported $ZnBr_2$ was prepared according to a modified literature procedure[6] : 40 g of silica gel was added to a solution of 10 g $ZnBr_2$ in 100 mL H_2O. The suspension was stirred for 30 minutes at room temperature. The silica was concentrated by rotatory evaporation until a fine powder was obtained. The humid silica was dried under vacuum under vigorous agitation at 110°C overnight. A slight orange coloration was observed due to the formation of Br_2.

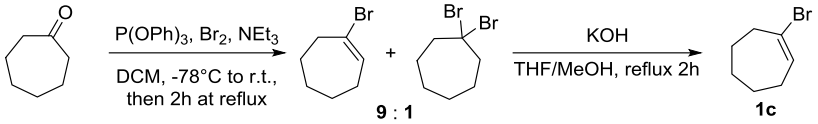
[5] Shi, J.-C.; Negishi E.-I. *Journal of Organometallic* **2003**, *687*, 518.
[6] Kodomari, M.; Nagaoka, T.; Furusawa, Y. *Tetrahedron Letters* **2001**, *42*, 3105.

2-bromooctanophenone (2b).



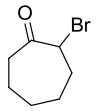
The title compound was obtained from **1b** (200.0 mg, 0.749 mmol) following the general oxidative hydrolysis procedure without added water. 207.3 mg of the α-bromoketone was isolated (98%) as a clear oil; R_f = 0.16 (1% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.03-8.01 (m, 2H), 7.63-7.57 (m, 1H), 7.52-7.46 (m, 2H), 5.13 (dd, *J* = 6.68, 7.65 Hz, 1H), 2.27-2.05 (m, 2H), 1.59-1.22 (m, 8H), 0.90-0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.3, 134.6, 133.7, 128.9, 128.8, 47.4, 33.6, 31.6, 28.9, 27.5, 22.6, 14.2; IR (neat) 2950, 2926, 2855, 1684, 1596, 1580, 1447 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{14}H_{19}BrONa$ $[MNa]^+$ 305.0511, found 305.0514.

(*E*)-1-bromocycloheptene (1c).



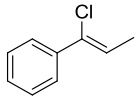
The compound was obtained from cycloheptanone (5.4 mL, 44.6 mmol) following the same procedure used to obtain 1-bromo-3,4-dihydronaphtalene **(1e)** as a 9:1 mixture (5.2 g) of the title compound and *gem*-dibromocycloheptane. 3.8 g of the mixture was dissolved in THF (7 mL) and KOH (544 mg, 9.7 mmol). The solution was heated to reflux and a few drops of methanol were added until all the KOH pellets were dissolved. After 2 hours, the solution was allowed to cool to r.t. before crushed iced and aqueous saturated NH_4Cl were added consecutively. The aqueous layer was extracted with three portions of diethyl ether; the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated by rotatory evaporation to afford 3.3g of the title compound as clear oil (49% over two steps) that decomposed to an orange oil with brown deposits upon storage. Kept under inert atmosphere, away from light; R_f = 0.88 (hexanes, $KMnO_4$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.20 (t, *J* = 6.54 Hz, 1H), 2.70-2.66 (m, 2H), 2.08 (dd, *J* = 6.51, 11.22 Hz, 2H), 1.75-1.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 133.5, 126.3, 40.8, 30.8, 29.4, 26.5, 26.4; IR (neat) 2921, 2878, 2849, 1642, 841, 672 cm^{-1}; LRMS-EI (m/z) calcd for $C_7H_{11}Br$ $[M]^{+\cdot}$ 174.0044, C_7H_{11} $[M\text{-}Br]^+$ 95.0861, found 174.0, 95.1.

α-bromocycloheptanone (2c).[7]



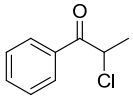
The title compound was obtained from **1c** (224.7 mg, 1.28 mmol) following the general oxidative hydrolysis procedure without added water. 78.3 mg of the title compound was isolated as a clear oil (32%); The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.38 (dd, J = 5.07, 9.56 Hz, 1H), 2.91-2.82 (m, 1H), 2.53-2.45 (m, 1H), 2.41-2.31 (m, 1H), 2.07-1.87 (m, 3H), 1.83-1.70 (m, 1H), 1.66-1.49 (m, 2H), 1.45-1.32 (m, 1H); HRMS ESI-Q-TOF (m/z) calcd for $C_7H_{11}BrONa$ $[MNa]^+$ 212.9885, found 212.9886.

(*Z*)-(1-Chloro-1-propenyl)benzene (1d).[8]



The title compound was obtained from propiophenone (10.3 g, 76.7 mmol) following a literature procedure (see **(*Z*)-(1-Chloro-1-butenyl)benzene) (1e)**). 6.5 g of the vinyl halide was obtained (56%) as a clear liquid; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.58-7.55 (m, 2H), 7.38-7.34 (m, 3H), 6.21 (q, J = 6.7 Hz, 1H), 1.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.6, 134.0, 128.5, 128.4, 126.5, 122.6, 15.3.

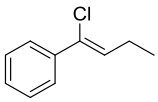
α-chloropropiophenone (2d).[9]



The title compound was obtained from **1d** (200 mg, 1.31 mmol) following the general oxidative hydrolysis procedure. 208.1 mg of the halide was isolated (94%) as a yellowish liquid; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.04-8.01 (m, 2H), 7.63-7.59 (m, 1H), 7.47-7.52 (m, 2H), 5.26 (q, J = 6.67 Hz, 1H), 1.75 (d, J = 6.66 Hz, 3H); HRMS ESI-Q-TOF calcd for C_9H_9ClONa $[MNa]^+$ 191.0234, found 191.0239.

[7] Basso, E. A. et al. *Spectrochimica Acta Part A* **2012,** *94*, 277.
[8] Kropp, P.J.; Crawford, S.D. *J. Org. Chem.* **1994**, *59*, 3102.
[9] Ahlsten, N.; Bermejo Gómez, A.; Martín-Matute, B. *Angew. Chem. Int. Ed*. **2013**, *52*, 6273.

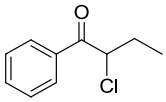
(*Z*)-(1-Chloro-1-butenyl)benzene (1e).



Acetyl chloride (5.8 mL, 81.0 mmol) was added to a solution of butyrophenone (1.5 g, 10.1 mmol) dissolved in anhydrous 1,2-DCE (10 mL, 1 M). While the solution was vigorously stirred, $ZnCl_2/SiO_2$* (3 g, 5.2 mmol) was slowly added. After one hour, the solution was filtered. The filter cake was washed with dichloromethane. The diluted solution was washed with three portions of saturated sodium bicarbonate or until CO_2 bubbling was no longer observed. The aqueous phase was extracted with three portions of dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated by rotatory evaporation. The crude was purified by flash chromatography (0.5% Et_2O in pentane). 1.4 g of the vinyl halide was isolated (85%) as a bright yellow liquid; R_f = 0.63 (hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.65-7.58 (m, 2H), 7.44-7.32 (m, 3H), 6.19 (t, J = 6.98 Hz, 1H), 2.47 (p, J = 7.50 Hz, 2H), 1.17 (t, J = 7.57 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.4, 132.4, 129.4, 128.3, 128.2, 126.4, 23.1, 13.1; IR (neat) 3082, 3054, 3019, 2968, 2936, 2871 cm^{-1}; LRMS-EI (m/z) calcd for $C_{10}H_{11}Cl$ $[M]^{+\cdot}$ 166.0549, $C_{10}H_{11}$ $[M\text{-}Cl]^+$ 131.0861, found. 166.1, 131.1.

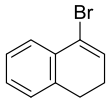
*Silica gel supported $ZnCl_2$ was prepared according to a modified literature procedure[6] : 40 g of silica gel was added to a solution of 10 g $ZnCl_2$ in 100 mL H_2O. The suspension was stirred for 30 minutes at room temperature. The silica was concentrated by rotatory evaporation until a fine powder was obtained. The humid silica was dried under vacuum under vigorous agitation at 130°C overnight.

α-chlorobutyrophenone (2e).



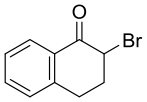
The title compound was obtained from **1e** (200.0 mg, 1.20 mmol) following the general oxidative hydrolysis procedure. 204.6 mg of the α-chloroketone was obtained (93%) as a clear yellowish oil; R_f = 0.33 (5% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.03 (m, 2H), 7.64-7.58 (m, 1H), 7.52-7.47 (m, 2H), 5.09 (dd, J = 5.75, 7.86 Hz, 1H), 2.27-1.97 (m, 2H), 1.10 (t, J = 7.35 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.6, 134.7, 133.8, 128.9, 128.8, 59.4, 27.1, 10.9; IR (neat) 2972, 2937, 2878, 1687, 1596, 1448, 685 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{10}H_{11}ClONa$ $[MNa]^+$ 205.0391, found 205.0397.

1-bromo-3,4-dihydronaphtalene (1f).



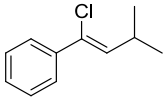
To a solution of triphenylphosphite (1.85 mL, 7 mmol) in anhydrous dichloromethane (20 mL) at -78°C were added bromine (400 µL, 7.7 mmol), anhydrous triethylamine (1.2 mL, 8.4 mmol) and α-tetralone (936 mg, 6.4 mmol) under nitrogen flow. Fumes were observed during the addition of triethylamine suggesting contamination by HBr contained in the previously added bromine. The solution was allowed to stir at room temperature for 20 hours. The solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ and with a saturated aqueous solution of NH_4Cl, the organic phase was dried over magnesium sulfate and concentrated by rotatory evaporation to yield a dark orange oil. The crude was purified by flash chromatography (pentane) to yield the title compound (57%) as a clear oil; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.58-7.55 (m, 1H), 7.29-7.18 (m, 2H), 7.12-7.10 (m, 1H), 6.46 (t, *J* = 4.83 Hz, 1H), 2.85 (t, *J* = 8.06 Hz, 2H), 2.38 (td, J = 8.40, 4.86 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 136.4, 133.2, 130.9, 128.4, 127.4, 126.9, 126.6, 121.5, 27.8, 25.6.

2-bromo-1,2,3,4-tetrahydronaphthalen-1-one (2f).[10]



The title compound was obtained from **1f** (246.4 mg, 1.18 mmol) following the general oxidative hydrolysis procedure without added water. 217.4 mg of the title compound was isolated as a clear oil (82%); The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.04 (d, *J* = 7.84 Hz, 1H), 7.48 (td, *J* = 1.36, 7.51 Hz, 1H), 7.32-7.23 (m, 2H), 4.69 (t, *J* = 4.28 Hz, 1H), 3.31-3.20 (m, 1H), 2.88 (dt, *J* = 4.43, 17.16 Hz), 2.54-2.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 190.5, 143.0, 134.1, 129.8, 128.8, 128.5, 127.0, 50.6, 31.8, 26.1.

(*Z*)-1-chloro-3-methyl-1-buten-1-yl)benzene (1g).

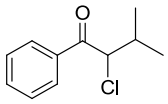


The title compound was obtained from isovalerophenone (1.0 g, 6.2 mmol) following a literature procedure (see **(Z)-(1-Chloro-1-butenyl)benzene) (1e)**). 1.0 g of the corresponding vinyl halide was isolated (92%) as a clear liquid; R_f = 0.71 (0.5% AcOEt in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$):

[10] Podgoršeka, A.; Stavbera, S.; Zupanb, M.; Iskraa, J. *Tetrahedron* **2009**, *65*, 4429.

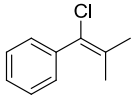
δ (ppm) 7.59-7.54 (m, 2H), 7.37-7.29 (m, 3H), 5.96 (d, J = 8.79 Hz, 1H), 2.98 (ddt, J = 6.71, 8.77, 13.41 Hz, 1H), 1.11 (d, *J* = 6.71 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.5, 135.0, 130.9, 128.4, 128.3, 126.5, 29.4, 22.1; IR (neat) 2961, 2927, 2868, 1444, 755, 690, 665 cm^{-1}; LRMS-EI (m/z) calcd for $C_{11}H_{13}Cl$ $[M]^{+\cdot}$ 181.0706, $C_{11}H_{13}$ $[M\text{-}Cl]^+$ 145.1017, found 181.1, 145.1.

α-chloroisovalerophenone (2g).



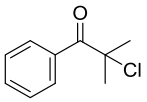
The title compound was obtained from **1g** (200.0 mg, 1.27 mmol) following the general oxidative hydrolysis procedure. 217.4 mg of the α-chloroketone was obtained (100%) as a clear oil; R_f = 0.34 (5% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.02-7.99 (m, 2H), 7.65-7.60 (m, 1H), 7.54-7.49 (m, 2H), 4.97 (d, *J* = 7.29 Hz, 1H), 2.55-2.44 (m, 1H), 1.14 (t, *J* = 6.64 Hz, 3H), 1.06 (t, *J* = 6.67 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 194.1, 135.3, 133.8, 128.94, 128.87, 65.1, 31.7, 21.3, 18.6; IR (neat) 2967, 2933, 2873, 1596, 1690, 1447 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{11}H_{13}ClONa$ $[MNa]^+$ 219.0547, found 219.0549.

α-chloro-β,β-dimethylstyrene (1h).[11]



The title compound was obtained from *iso*-butyrophenone (502.6 mg, 3.39 mmol) following a literature procedure (see **(Z)-(1-Chloro-1-butenyl)benzene) (1e)**). 466.7 mg of the vinyl halide was obtained (75%) as a yellow liquid; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38-7.26 (m, 5H), 2.01 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 139.5, 130.7, 129.4, 128.2, 127.9, 125.4, 22.0, 22.1.

2-chloro-2-methyl-1-phenylpropanone (2h).[12]

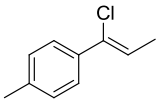


The title compound was obtained from **1h** (200.0 mg, 1.20 mmol) following the general oxidative hydrolysis procedure but heating at 40°C for 3 days. 167.6 mg of the α-chloroketone was obtained

[11] Lauritzen, S. E.; Rømming, C.; Skattebøl, L. *Acta Chemica Scandinavica B* **1981**, *35*, 263.
[12] Guthrie, J. P.; Cossar, J. *Can. J. Chem*. **1990**, *68*, 397.

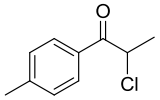
(76%) as a clear liquid; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.16-8.13 (m, 2H), 7.60-7.50 (m, 1H), 7.49-7.40 (m, 2H), 1.89 (s, 6H). HRMS ESI-Q-TOF (m/z) calcd for $C_{10}H_{11}ClONa$ $[MNa]^+$ 205.0391, found 205.0392.

(*Z*)-1-(4-methylphenyl)-1-chloropropene (1i).



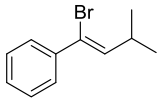
The title compound was obtained from 4'-methylpropiophenone (1.5g, 10.1 mmol) following a literature procedure (see **(*Z*)-(1-Chloro-1-butenyl)benzene) (1e)**). 912 mg of the corresponding vinyl halide (Z : E = 95 : 5 as determined by integration ratios) was isolated (54%) as a bright yellow liquid; R_f = 0.60 (hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51-7.48 (m, 2H), 7.20-7.17 (m, 2H), 6.20 (q, J = 6.70 Hz, 1H), 2.40 (s, 3H), 1.98 (d, J = 6.71 Hz, 3H); Characteristic shifts for the E isomer: 6.05 (q, J = 7.30 Hz, 1H), 2.41 (s, 3H), 1.77 (d, J = 7.31 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.1, 135.7, 129.0, 126.3, 121.5, 21.2, 15.2; IR (neat) 3027, 2917, 2855 cm^{-1}; LRMS-EI (m/z) calcd for $C_{10}H_{11}Cl$ $[M]^{+\cdot}$ 166.0549, $C_{10}H_{11}$ $[M\text{-}Cl]^+$ 131.0861, found 166.1, 131.1.

α-chloro-4-methylpropiophenone (2i).



The title compound was obtained from **1i** (200.0 mg, 1.20 mmol) following the general oxidative hydrolysis procedure. 197.5 mg of the α-chloroketone was obtained (90%) as yellow crystals; T_{fus} 48-50°C; R_f = 0.27 (4% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 8.27 Hz, 2H), 7.29 (d, J = 7.99 Hz, 2H), 5.24 (q, J = 6.67 Hz, 1H), 2.43 (s, 3H), 1.74 (d, J = 6.67 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.4, 144.9, 131.7, 129.6, 139.2, 52.9, 21.8, 20.2; IR (neat) 3066, 2984, 2931, 2865, 1681, 1605 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{10}H_{11}ClONa$ $[MNa]^+$ 205.0390, found 205.0392.

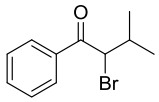
(*Z*)-(1-bromo-3-methylbut-1-enyl)benzene (1j).



To an unsealed round-bottom flask were added 2-methylbutyrophenone (2.19 g, 13.5 mmol) and trifluoroacetic acid (14 mL). The solution was stirred in an ice bath. Acetyl bromide (8 mL, 108 mmol) was carefully added over 120 minutes. The solution was allowed to warm to r.t. and was stirred during

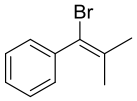
36 hours. The solution was carefully poured over crushed ice. Once all the ice had melted, the aqueous layer was extracted with pentane, the combined organic layers were washed several times with saturated sodium bicarbonate, dried over magnesium sulfate, filtered, concentrated by rotatory evaporation and dried under vacuum while stirred to yield 2.9 g of a brown oil. The crude was purified by flash chromatography (3% EtOAc in pentane). 2.09 g of the vinyl halide was isolated (69%) as a yellow oil; R_f = 0.70 (0.5% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.54-7.51 (m, 2H), 7.35-7.25 (m, 3H), 6.22 (d, *J* = 8.65 Hz, 1H), 2.90 (dsept, *J* = 8.63, 6.71 Hz, 1H), 1.11 (t, *J* = 6.70 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 140.1, 138.6, 128.34, 128.29, 127.7, 123.2, 32.3, 21.9; IR (neat) 2959, 2929, 2864, 1629, 1443 cm^{-1}; LRMS-EI (m/z) calcd for $C_{11}H_{13}Br$ $[M]^{+\cdot}$ 224.0201, $C_{11}H_{13}$ $[M\text{-}Br]^+$ 145.1017, found 224.0, 145.1.

α-bromoisovalerophenone (2j).[13]



The title compound was obtained from **1j** (270.1 mg, 1.20 mmol) following the general oxidative hydrolysis procedure without added water. 280.0 mg of the α-bromoketone was isolated (97%) as yellowish oily crystals; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.02-7.98 (m, 2H), 7.63-7.57 (m, 1H), 7.52-7.47 (m, 2H), 4.94 (d, *J* = 8.61 1H), 2.48 (dsept, *J* = 8.55, 6.60 Hz, 1H), 1.21 (d, *J* = 6.61 Hz, 3H), 1.03 (d, *J* = 6.61 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.8, 135.1, 133.8, 128.94, 128.88, 56.0, 31.2, 20.8, 20.6.

α-Bromo-β,β-dimethylstyrene (1k).[14]

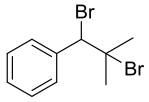


The title compound was prepared from a 3:1 mixture of 1,2-dibromo-2-methyl-1-phenylpropane and the title compound itself. KOH (126.5 mg, 2.26 mmol) was dissolved in EtOH (1 mL) and H_2O (0.07 mL) and heated to reflux. The solution was removed from the oil bath and 1,2-dibromo-2-methyl-1-phenylpropane mixed with the desired product (1:3, 2.9 g) was added at such a rate that the solution stayed at reflux without external heating. The solution was stirred at 60°C for 7 hours during which KBr precipitated. The solution was filtered to remove KBr. The filtrate was slowly poured in water. The aqueous phase was extracted with pentane. The combined organic fractions were dried over magnesium

[13] Kihara, M.; Ikeuchi, M.; Jinno, K.; Kashimoto, M.; Kobayashi, Y.; Nagao, Y. *Tetrahedron* **1993**, *49*, 1017.
[14] Robinson, L. R.; Burns, G. T.; Barton, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 3935.

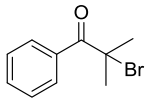
sulfate, filtered and concentrated by rotatory evaporation to yield a clear liquid. The crude was purified by flash chromatography (0-0.5% EtOAc in pentane). 2.5 g of the vinyl halide was isolated (61% over two steps); The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.37-7.27 (m, 4H), 2.05 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 141.3, 133.7, 129.5, 128.3, 127.8, 116.9, 25.4, 22.1.

1,2-dibromo-2-methyl-1-phenylpropane.[15]



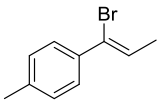
The title compound was obtained from isobutyrophenone (2 g, 13.5 mmol) following a literature procedure (see **(*Z*)-1-bromo-1-phenyloctene (1b)**). 2.9 g of the corresponding dihalide was obtained along with its elimination product α-Bromo-β,β-dimethylstyrene, as a clear liquid; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.52-7.45 (m, 2H), 7.35-7.30 (m, 3H), 5.26 (s, 1H), 2.02 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.6, 130.1, 128.7, 67.4, 65.3, 34.2, 30.4.

2-bromo-2-methyl-1-phenylpropanone (2k).



The title compound was obtained from **1k** (253.3 mg, 1.20 mmol) following the general oxidative hydrolysis procedure, without added water, over 15 hours at 40°C. 217.1 mg of the α-bromoketone was isolated (80%) as a clear liquid; R_f = 0.32 (5% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.18-8.15 (m, 2H), 7.59-7.53 (m, 1H), 7.49-7.42 (m, 2H), 2.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 196.9, 134.9, 132.4, 130.1, 128.2, 60.4, 31.6; IR (neat) 3005, 2975, 2927, 1673 cm^{-1}; HRMS ESI-Q-TOF (Maxis) (m/z) calcd for $C_{10}H_{11}BrONa$ $[MNa]^+$ 248.9885, found 296.9906.

(*Z*)-1-(4-methylphenyl)-1-bromopropene (1l).

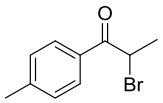


The title compound was obtained from 4'-methylpropiophenone (2.5 g, 16.9 mmol) following a literature procedure (see **(Z)-1-bromo-1-phenyloctene**). 2.1 g of the corresponding vinyl halide was isolated (58%) as a yellowish oil; R_f = 0.81 (1% EtOAc in hexanes UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ

[15] Yokoyama, Y.; Nagashima, H.; Man, S.; Yokoyama, S. Y.; Takada, K. *Bulletin of the Chemical Society of Japan*, **2003**, *76*, pp 355.

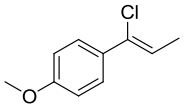
(ppm) 7.43 (d, J = 8.22 Hz, 2H), 7.15 (d, J = 8.23 Hz, 2H), 6.25 (q, J = 6.59 Hz, 1H), 2.37 (s, 3H), 1.96 (d, J = 6.60 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 138.3, 137.5, 129.0, 127.5, 126.8, 125.5, 21.2, 18.2; IR (neat) 3025, 2918, 2853, 797 cm^{-1}; LRMS-EI (m/z) calcd for $C_{10}H_{11}Br$ $[M]^{+\cdot}$ 210.0044, $C_{11}H_{13}$ $[M\text{-}Br]^+$ 131.0861, found 210.0, 131.1.

2-bromo-1-(*p*-tolyl)propiophenone (2l).



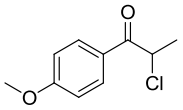
The title compound was obtained from **1l** (147.4 mg, 0.698 mmol) following the general oxidative hydrolysis procedure without added water. 147.4 mg of the α-bromoketone was isolated (93%) as white crystals; T_{fus} (from pentane/diethyl ether) 72-76°C; R_f = 0.57 (10% EtOAc in hexanes, UV); ^{1}H NMR 300 MHz, $CDCl_3$): δ (ppm) 7.93 (d, J = 8.29 Hz, 2H), 7.28 (d, J = 8.52 Hz, 2H), 5.28 (q, J = 6.64 Hz, 1H), 2.42 (s, 3H), 1.89 (d, J = 6.64 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.1, 144.8, 131.6, 129.6, 129.2, 41.7, 21.9, 20.1; IR (neat) 3008, 2992, 2926, 1677, 1606 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{10}H_{11}BrONa$ $[MNa]^+$ 248.9886, found 248.9902.

(*Z*)-1-chloro-1-(4-methoxyphenyl)-1-propene (1m).



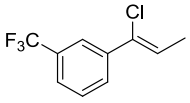
The title compound was obtained from *para*-methoxypropiophenone (1049 mg, 6.4 mmol) following a literature procedure (see **(*Z*)-(1-Chloro-1-butenyl)benzene) (1e)**) going from 0°C to r.t. instead of heating. 82 mg of the corresponding vinyl halide was isolated (7%, the low yield is attributed to the presence of remaining water in the silica gel-supported zinc chloride) as yellow crystals; T_{fus} (from pentane) 36-40°C; R_f = 0.57 (5% AcOEt in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51 (d, J = 8.90 Hz, 2H), 6.89 (d, J = 8.92 Hz, 2H), 6.11 (q, J = 6.70 Hz, 1H), 3.84 (s, 3H), 1.95 (d, J = 6.70 Hz, 3H). Caracteristic shifts for E isomer: 6.00 (q, J = 7.36 Hz, 1H), 1.75 (d, J = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 159.7, 133.6, 131.3, 127.7, 120.8, 113.7, 55.5, 15.2; IR (neat) 3038, 2959, 2938, 2911, 2880, 2843, 1676, 797 cm^{-1}; LRMS-EI (m/z) calcd for $C_{10}H_{11}ClO$ $[M]^{+\cdot}$ 182.0498, $C_{10}H_{11}O$ $[M\text{-}Cl]^+$ 147.0810, found 182.1, 147.1.

α-chloro-*p*-methoxypropiophenone (2m).



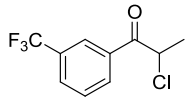
The title compound was obtained from **1m** (20.7 mg, 0.113 mmol) following the general oxidative hydrolysis procedure. 19.2 mg of the α-chloroketone was isolated (86%) as a clear oil; R_f = 0.25 (5% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.01 (d, J = 8.99 Hz, 2H), 6.96 (d, J = 8.99 Hz, 2H), 5.22 (q, J = 6.66 Hz, 1H), 1.73 (d, J = 6.66 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 192.4, 164.1, 131.5, 127.1, 114.1, 55.7, 52.8, 20.2; IR (neat) 2978, 2931, 2843, 1679, 1597, 1572, 1510, 1443 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{10}H_{11}ClO_2Na$ $[MNa]^+$ 221.0345, found 221.0341.

(*Z*)-1-chloro-1-(3-trifluoromethyl)-1-propene (1n).



The title compound was obtained from *para*-methoxypropiophenone (550 mg, 2.7 mmol) following a literature procedure (see **(*Z*)-(1-Chloro-1-butenyl)benzene) (1e)**). 275 mg of the corresponding vinyl halide was isolated (52%) as yellow oil; R_f = 0.70 (5% Et_2O in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.81 (s, 1H), 7.74 (d, J = 7.78 Hz, 1H), 7.55 (d, J = 7.77 Hz, 1H), 7.46 (t, J = 7.78 Hz, 1H), 6.29 (q, J = 6.72 Hz, 1H), 1.98 (d, J = 6.72 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 139.1, 132.4, 130.8 (q, J = 32.4 Hz), 129.4, 128.8, 124.8 (q, J = 3.8 Hz), 124.2, 124.0 (q, J = 270.5 Hz), 123.1 (q, J = 3.9 Hz), 15.2; IR (neat) 3076, 3038, 2919, 2862, 1328, 1122 cm^{-1}; LRMS-EI (m/z) calcd for $C_{10}H_8ClF_3$ $[M]^{+\cdot}$ 220.0267, C_9H_8Cl $[M\text{-}CF_3]^+$ 151.0315, $C_{10}H_8F_3$ $[M\text{-}Cl]^+$ 185.0578, found 220.0, 151.0, 185.1.

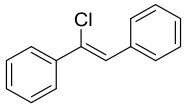
α-chloro-*m*-(trifluoromethyl)propiophenone (2n).



The title compound was obtained from **1n** (144.7 mg, 0.656 mmol) following the general oxidative hydrolysis procedure. 98.5 mg of the α-chloroketone was isolated (63%) as a yellowish liquid; R_f = 0.44 (5% Et_2O in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.28 (s, 1H), 8.21 (d, J = 7.86 Hz, 1H), 7.86 (d, J = 7.81 Hz, 1H), 7.65 (t, J = 7.83Hz, 1H), 5.22 (q, J = 6.63 Hz, 1H), 1.77 (d, J = 6.63 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 192.3, 134.7, 132.1, 131.5 (q, J = 33.1 Hz), 130.1 (q, J = 3.5 Hz), 129.4, 125.9 (q, J = 3.8 Hz), 123.6 (q, J = 272.6 Hz), 52.6, 19.6; IR (neat) 3081, 2983, 2929,

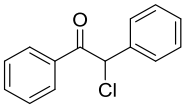
2857, 1698, 1324 cm^{-1}; LRMS-EI (m/z) calcd for $C_{10}H_8ClF_3O$ $[M]^{+\cdot}$ 236.0216, $C_8H_4F_3O$ $[CF_3PhCO]^+$ 173.0214, $C_7H_4F_3$ $[CF_3Ph]^+$ 145.0263, found 236.0, 173.0, 145.0.

(*Z*)-(1-chloroethene-1,2-diyl)dibenzene (1o).[16]



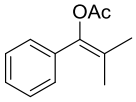
The title compound was obtained from phenylacetophenone (1000.0 mg, 5.10 mmol) following a literature procedure (see **(*Z*)-(1-Chloro-1-butenyl)benzene) (1e)**). 923.9 mg of the vinyl halide was isolated (84%) as yellow crystals; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.82-7.67 (m, 4H), 7.47-7.29 (m, 6H), 7.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 139.4, 135.4, 132.3, 129.6, 128.9, 128.6, 128.5, 128.2, 126.9, 126.3.

α-chlorophenylacetophenone (2o).[17]



The title compound was obtained from **1o** (306.2 mg, 1.426 mmol) following the general oxidative hydrolysis procedure. 261.6 mg of the title compound was obtained (80%) as yellow crystals; The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.02-7.91 (m, 2H), 7.59-7.29 (m, 8H), 6.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 191.6, 136.0, 134.4, 133.9, 129.33, 129.30, 129.27, 128.9, 128.6, 62.4; HRMS ESI-Q-TOF (m/z) calcd for $C_{14}H_{11}ClONa$ $[MNa]^+$ 253.0391, found 253.0390.

2-methyl-1-phenyl-1-acetoxy-1-propene (1p).[18]

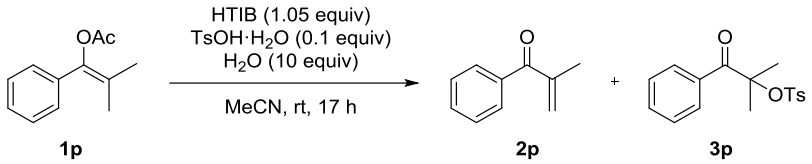


To a solution of DIPA (3.4 mL, 24.3 mmol) in anhydrous THF (101 mL) previously cooled to -78°C was slowly added *n*-BuLi 2.2M (11 mL). The solution was allowed to reach r.t. at which it was stirred for 30 minutes. It was cooled to -78°C and isobutyrophenone (3g, 20.2 mmol) was slowly added. Again, the solution was allowed to reach r.t. at which it was stirred for 30 minutes. It was cooled to -78°C and acetic anhydride (3.9 mL, 40.5 mmol) was carefully added. The solution turned into a viscous gel which

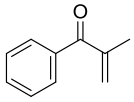
[16] Su, W.; Jin, C. *Org. Lett*. **2007**, *9*, 993-996.
[17] Ruan, L.; Shi, M.; Li, N.; Ding, X.; Yang, F.; Tang, J. *Org. Lett.* **2014**, *16*, 733.
[18] Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasooriya, N. *Eur. J. Org. Chem*. **2003**, 634.

was stirred overnight while reaching r.t. The solution was diluted with EtOAc, the organic layer was washed with saturated sodium bicarbonate, twice, and with brine, once. The organic phase was dried over sodium sulfate, filtered and concentrated by rotatory evaporation to yield 5.7 g of orange oil. It was purified by flash chromatography (2%-5% EtOAc in pentane). 1.9 g of the title compound was isolated as an oil (50%); The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.35-7.26 (m, 5H), 2.15 (s, 3H), 1.80 (s, 3H), 1.75 (s, 3H); HRMS ESI-Q-TOF (m/z) calcd for $C_{12}H_{14}O_2Na$ $[MNa]^+$ 213.0886, found 213.0891.

Supplementary reaction, reaction of enol ester 1p.

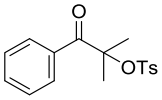


2-methyl-1-phenyl-prop-1-en-1-one (2p).[19]



The title compound was obtained as the major product of the reaction to produce β,β-dimethyl-β-toxyloxyacetophenone. 52.3 mg of the enone was isolated as a clear oil (34%); The characterization data is consistent with the reported data in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.74-7.69 (m, 2H), 7.55-7.49 (m, 1H), 7.45-7.39 (m, 2H), 5.90 (s, 1H), 5.61 (s, 1H), 2.06 (s, 3H); HRMS ESI-Q-TOF (m/z) calcd for $C_{10}H_{11}O$ $[MH]^+$ 147.0804, found 147.0810.

β,β-dimethyl-β-toxyloxyacetophenone (3p).

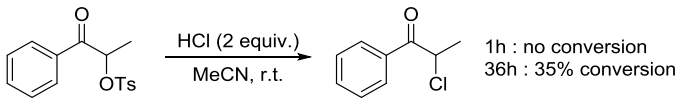


The title compound was obtained from **1p** (197.9 mg, 1.04 mmol) following the general oxidative hydrolysis procedure. 30.9 mg of the α-tosyloxyketone was isolated as a white solid (9%); R_f = 0.18 (10% EtOAc in hexanes, UV); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.05-8.02 (m, 2H), 7.56-7.50 (m, 3H), 7.41-7.36 (m, 2H), 7.24-7.21 (m, 2H), 2.42 (s, 3H), 1.84 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 198.2, 144.7, 135.5, 134.2, 132.9, 130.0, 129.6, 128.4, 127.6, 92.0, 26.5, 21.7; IR (neat) 3072,

[19] Liu, J.; Ma, S. *Org. Lett.* **2013**, *15*, 5150.

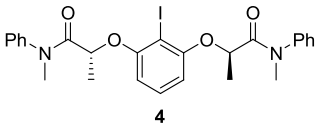
2920, 1762, 1675, 1337, 1175, 693 cm^{-1}; HRMS ESI-Q-TOF (m/z) calcd for $C_{17}H_{18}O_4SNa$ $[MNa]^+$ 341.0826, found 341.0825.

Supplementary reaction, halide S_N2 displacement on α-tosyloxypropiophenone.

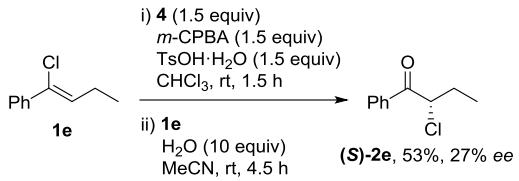


To a 20 mL vial were added α-tosyloxypropiophenone (48.4 mg, 0.159 mmol), CD_3CN (0.53 mL) and 12M HCl (26 □L, 0.318 mmol). Evolution of α-chloropropiophenone was determined by integration ratios of ^1H NMR (300 MHz, 5 seconds relaxation time). After an hour, no conversion was observed. After 36 hours, a conversion of 35% is observed.

Enantioselective protocol.



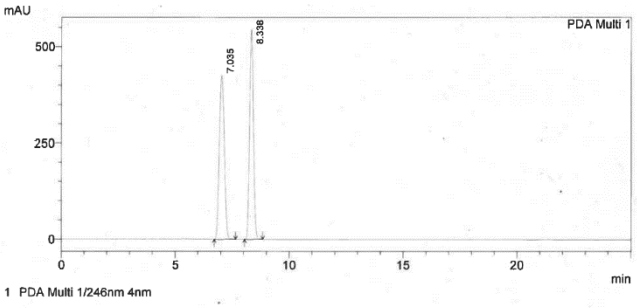
4



To a round-bottom flask were added **4**[20] (125.9 mg, 0.225 mmol), *m*-CPBA 77% (50.5 mg, 0.225 mmol), *p*-TsOH·H_2O (42.8 mg, 0.225 mmol) and chloroform (225 □L). The reaction mixture was stirred at room temperature for an hour before it was evaporated by rotatory evaporation. A solution of **1e** (20.0 mg, 0.120 mmol) in acetonitrile (0.6 mL) with H_2O (21.6 □L, 1.20 mmol) was added to the residue and was stirred at room temperature for 4.5 hours (incomplete reaction). The reaction mixture was diluted in water and extracted thrice with Et_2O. The organic layer was washed with brine, dried of magnesium sulfate and concentrated by rotatory evaporation to yield 171.9 mg of yellow crystals. The crude product was purified by flash chromatography on silica-gel (0.1%-1% Et_2O in pentane). 11.6 mg of **2e** was isolated (53% and 27% *ee*). The enantiomeric excess was determined by HPLC analysis on the purified product: Chiracel **OD-H** column, 95.5:0.5 hexanes/*i*-PrOH, 1.0 mL/min, t_r = 7.0 min (*R*), t_r = 8.3 min (*S*). The absolute configuration was determined by analogy to (*S*)-2-Chloro-1-phenyl-propan-1-one separation on the same chiral column.[21]

[20] Basdevant, B.; Legault, C. Y. *Org. Lett.* **2015**, *17*, 4918.
[21] Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240.

Racemic

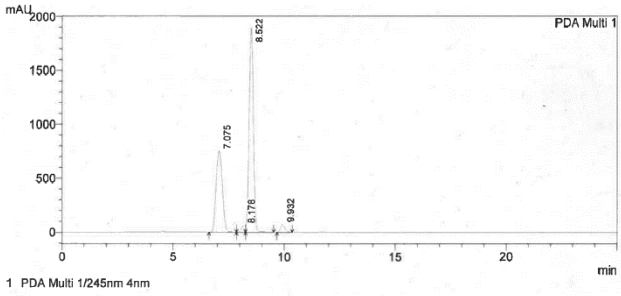


PeakTable

PDA Ch1 246nm 4nm

Peak#	Ret. Time	Area	Area %
1	7.035	6529941	50.012
2	8.338	6526875	49.988
Total		13056816	100.000

Enantioselective reaction



PeakTable

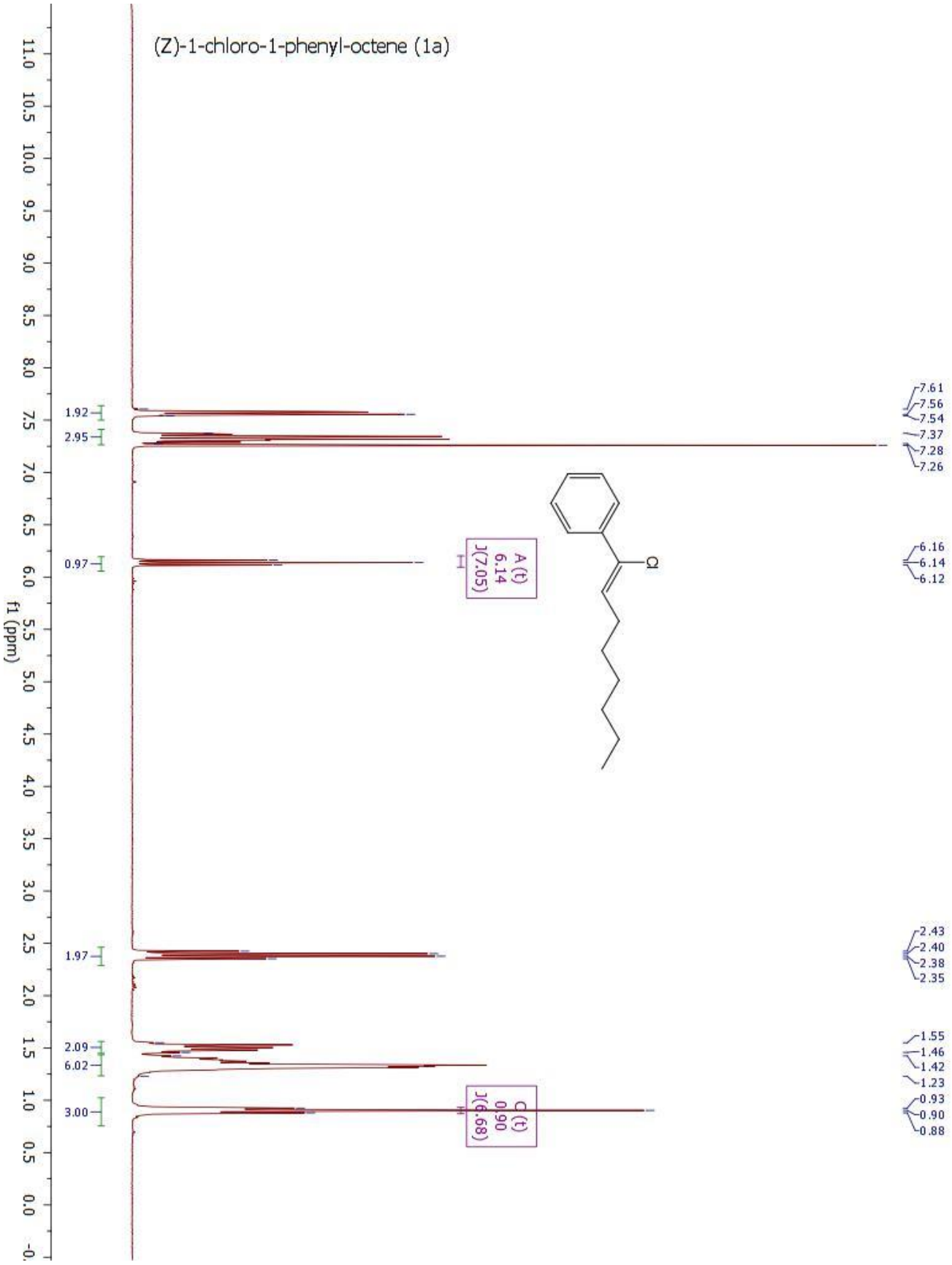
PDA Ch1 245nm 4nm

Peak#	Ret. Time	Area	Area %
1	7.075	14637823	35.113
2	8.178	754800	1.811
3	8.522	25316191	60.729
4	9.932	978643	2.348
Total		41687458	100.000

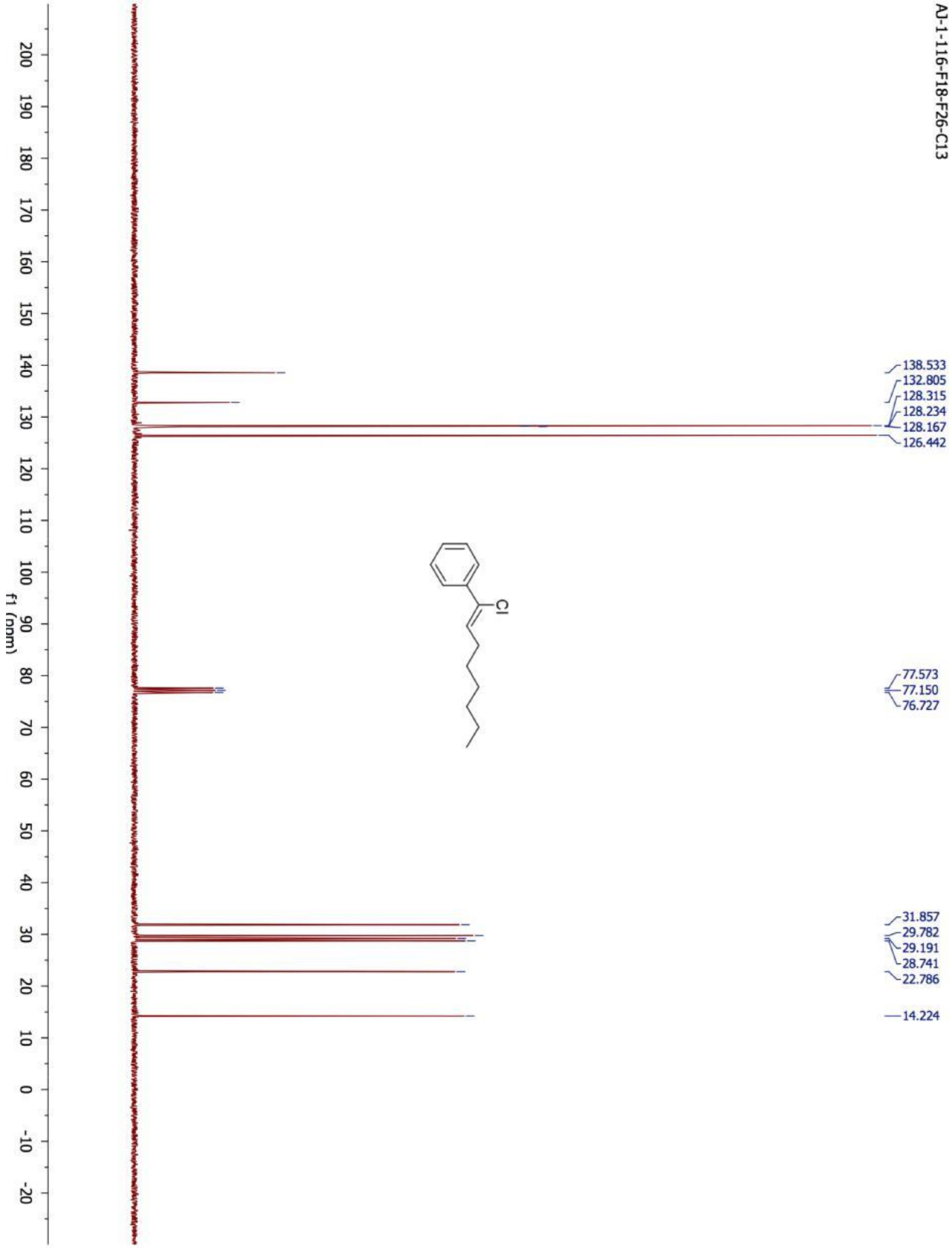
36.639
63.368

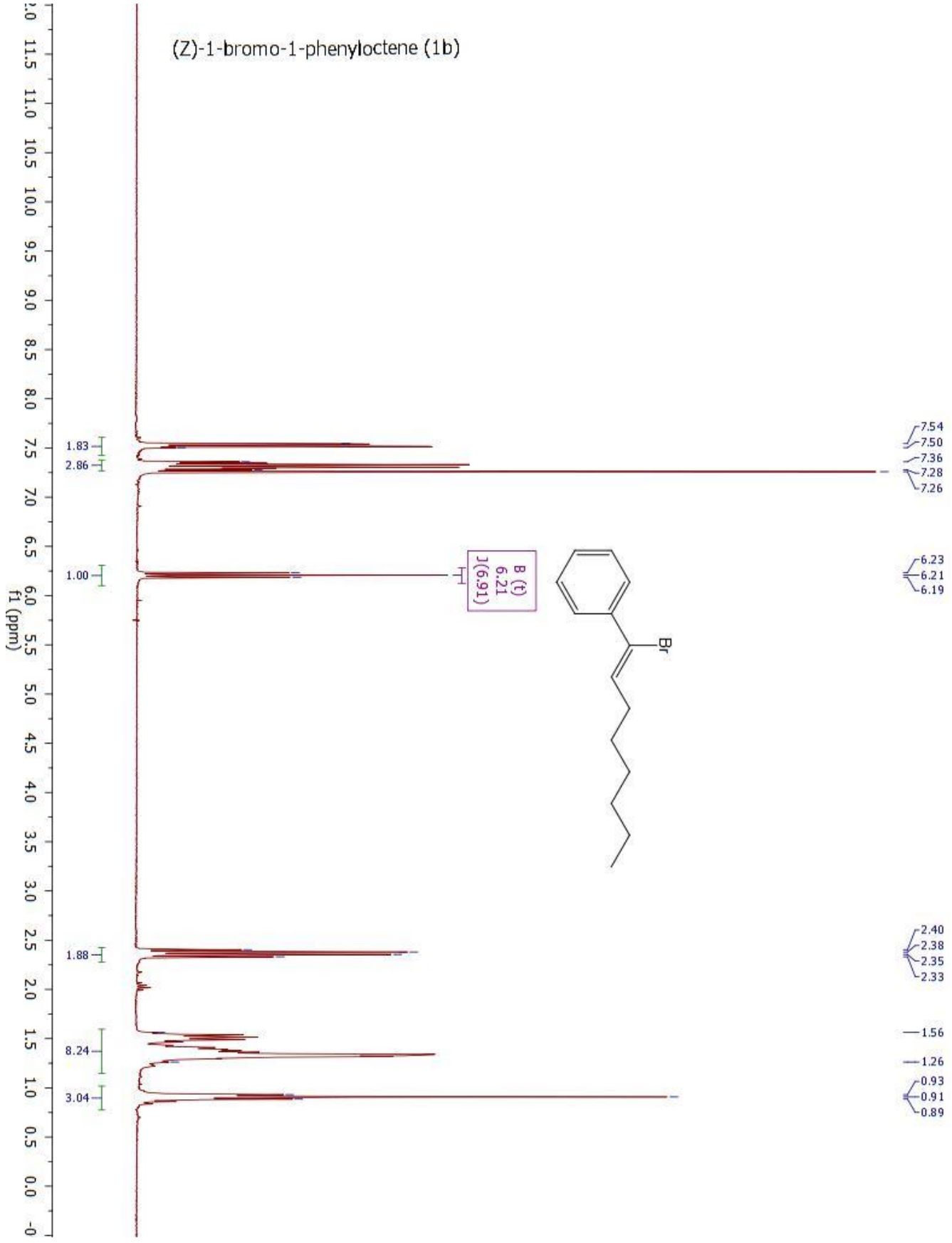
27% ee

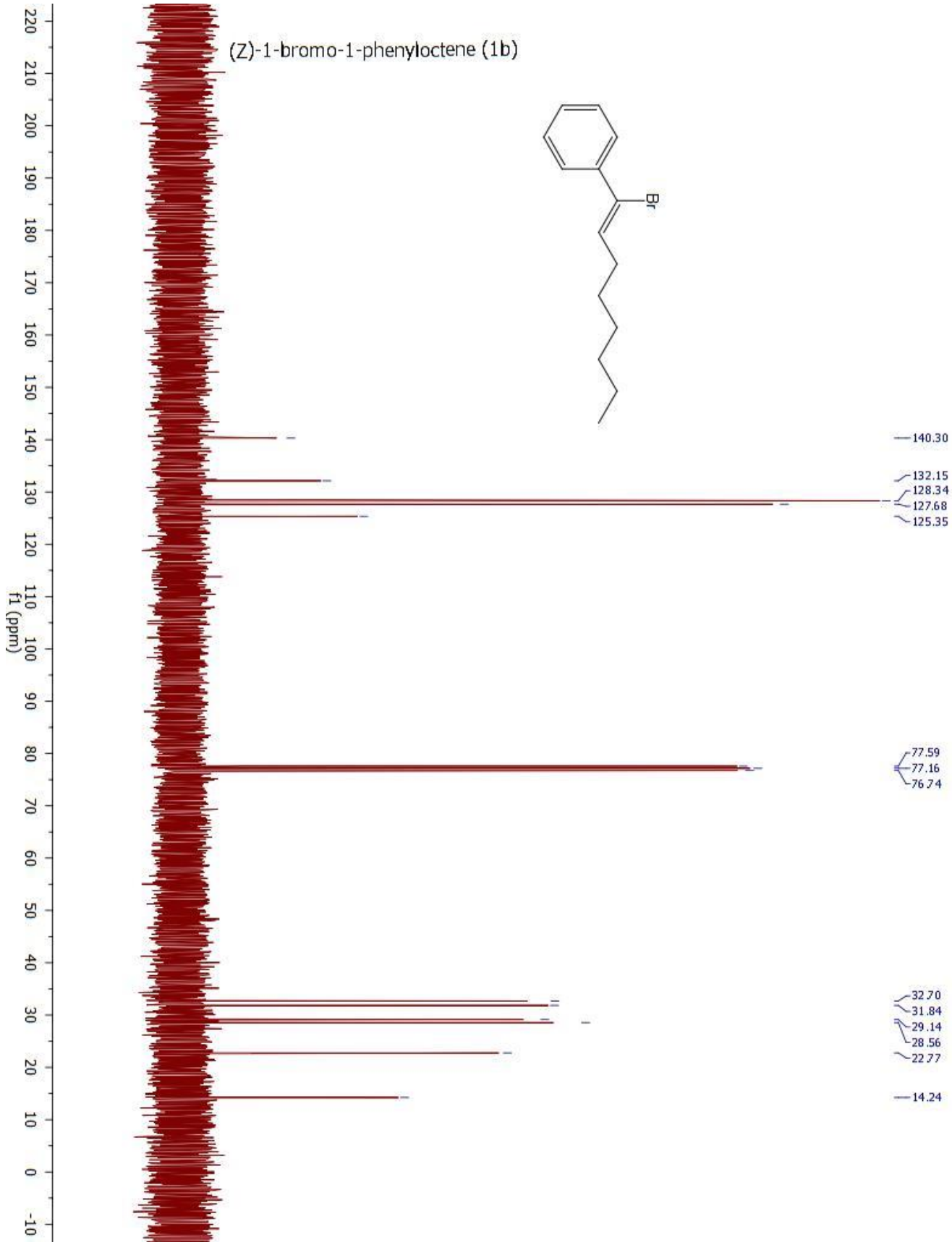
ANNEXE 2 : SPECTRES DE RÉSONANCE MAGNÉTIQUE NUCLÉAIRE DES PROTONS

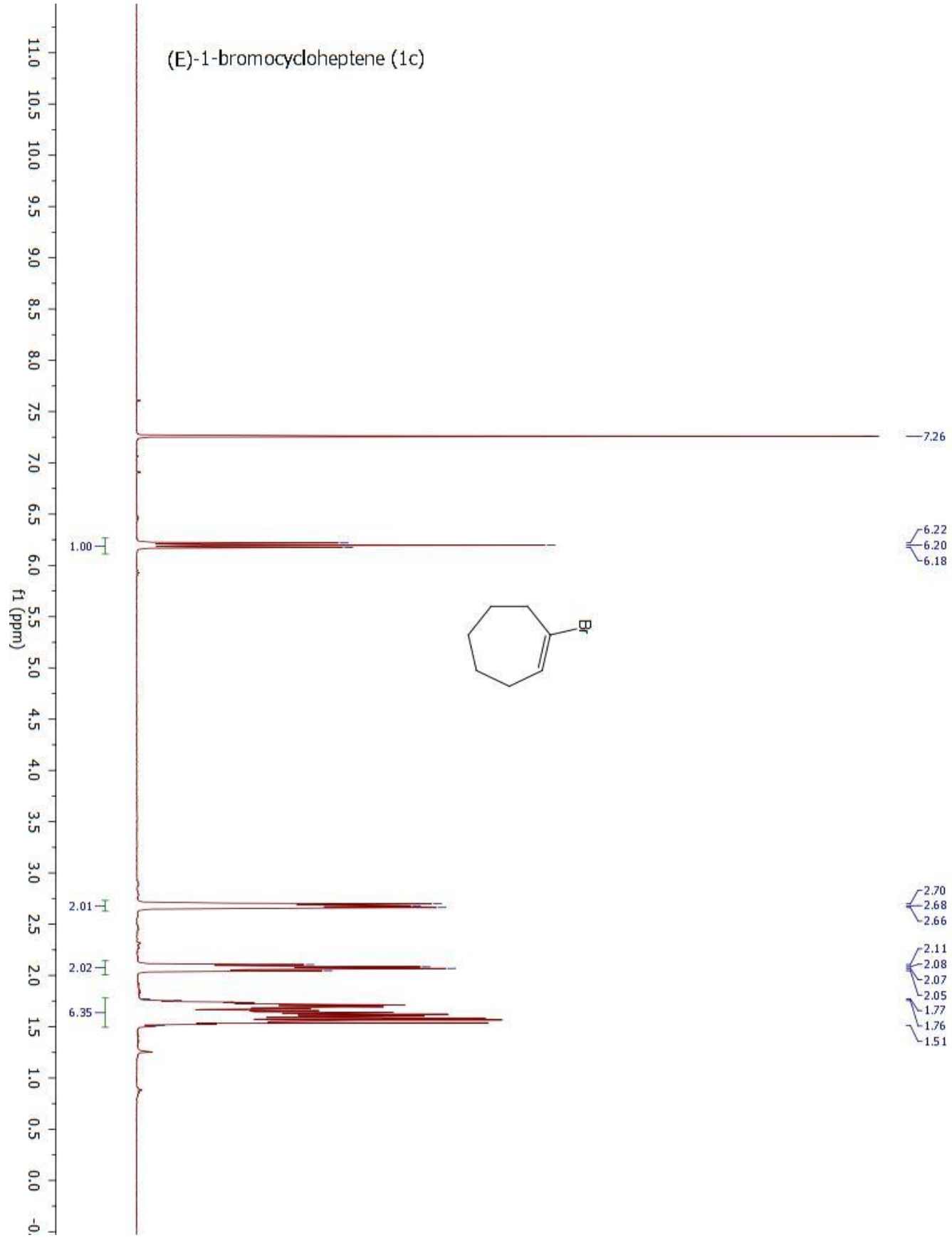

(Z)-1-chloro-1-phenyl-octene (1a)
f1 (ppm)
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
1.92
2.95
0.97
1.97
2.09
6.02
3.00
A (t)
6.14
J(7.05)
C (t)
0.90
J(6.68)
Cl
7.61
7.56
7.54
7.37
7.28
7.26
6.16
6.14
6.12
2.43
2.40
2.38
2.35
1.55
1.46
1.42
1.23
0.93
0.90
0.88

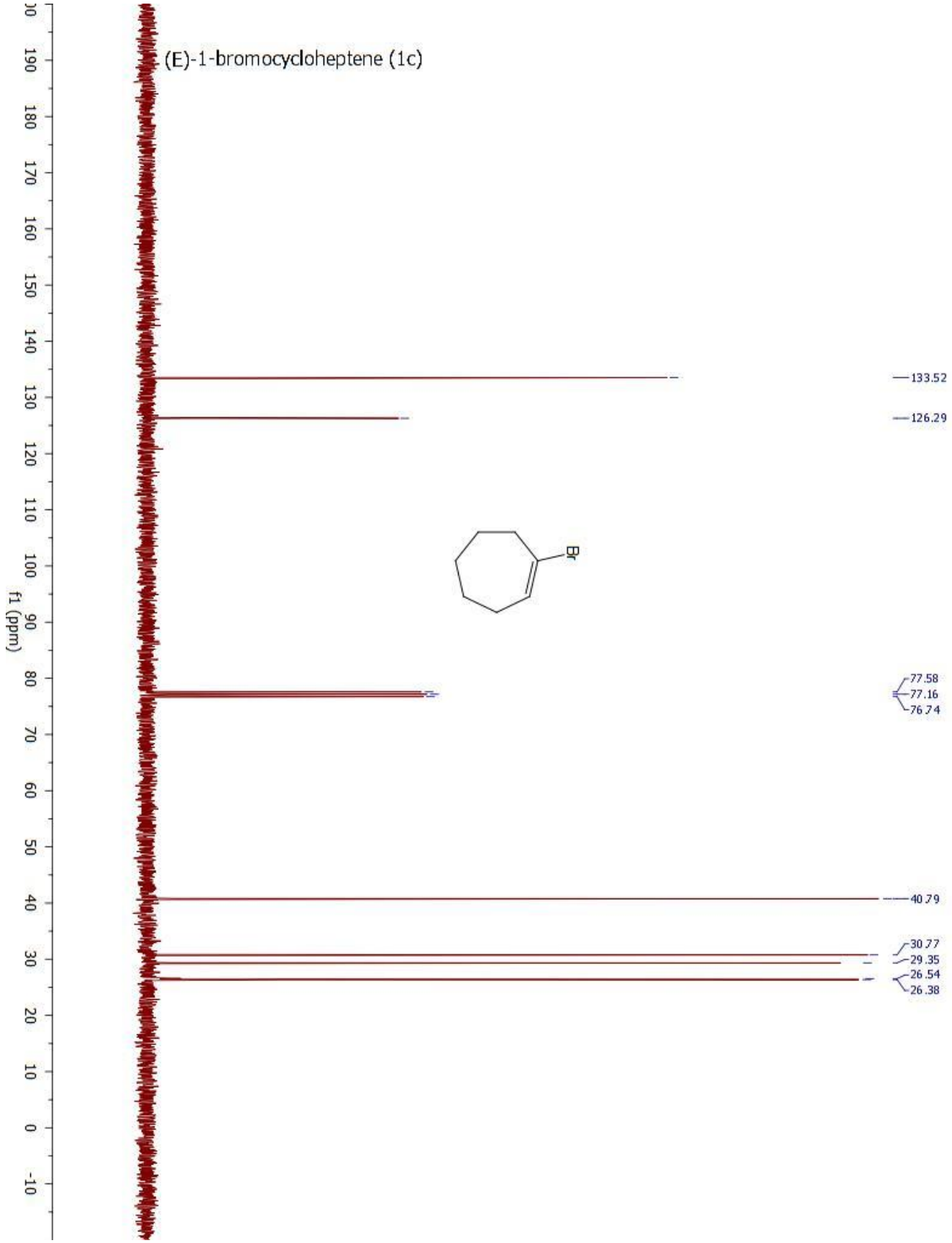
(Z)-1-chloro-1-phenyl-octene (1a)

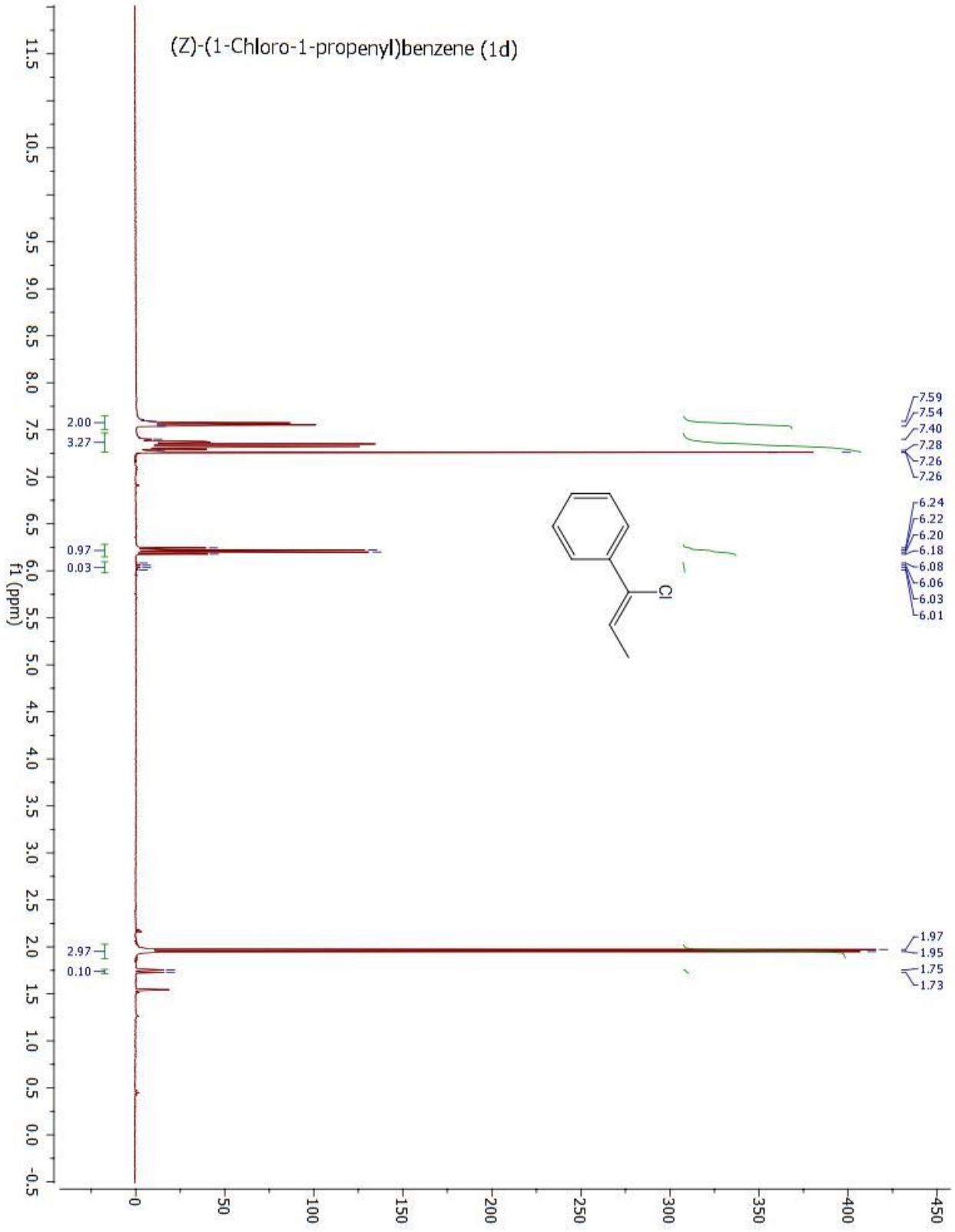



(Z)-1-bromo-1-phenyloctene (1b)
f1 (ppm)
1.83
2.86
1.00
1.88
8.24
3.04
B (t)
6.21
J(6.91)
Br
7.54
7.50
7.36
7.28
7.26
6.23
6.21
6.19
2.40
2.38
2.35
2.33
1.56
1.26
0.93
0.91
0.89

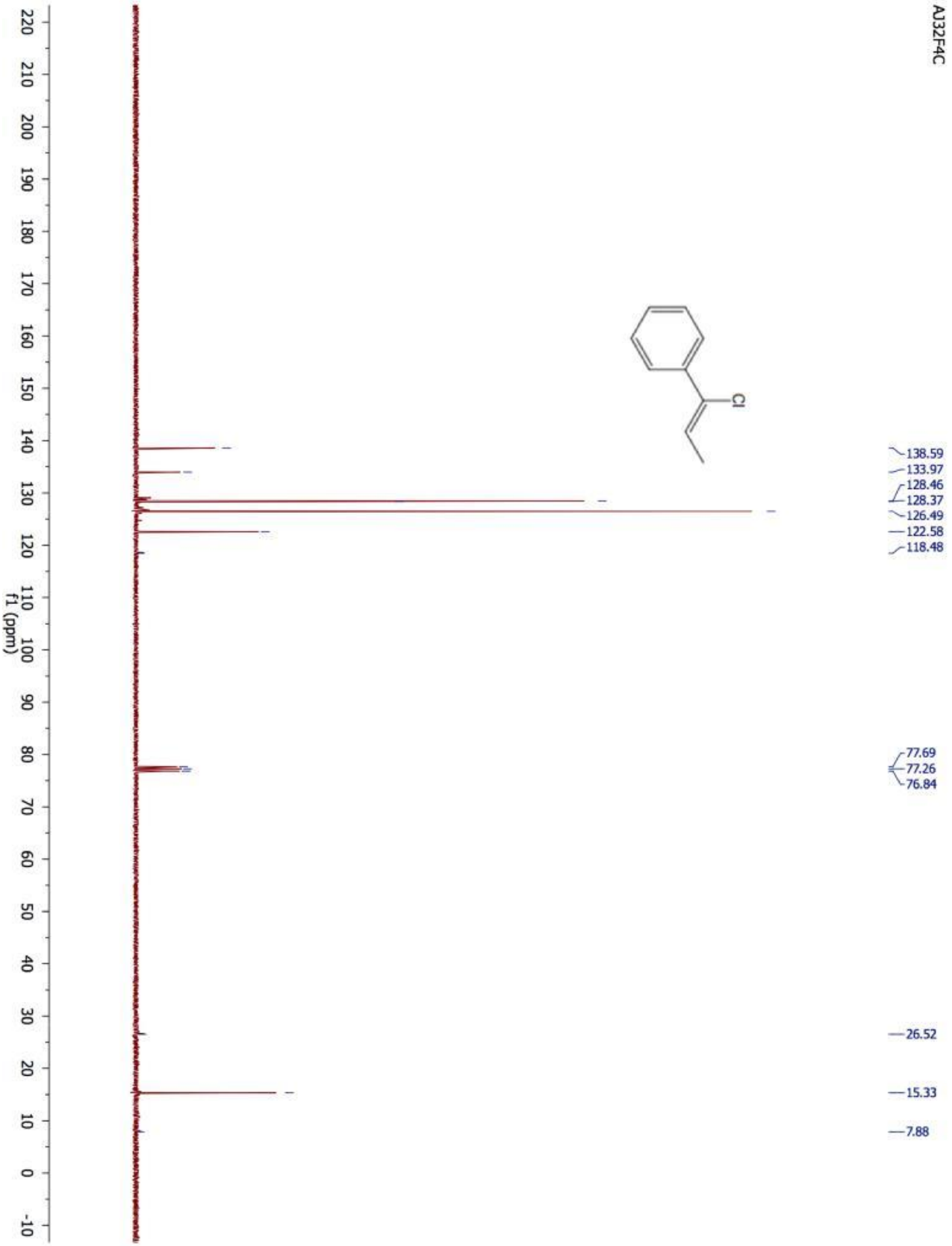

(Z)-1-bromo-1-phenyloctene (1b)
Br
140.30
132.15
128.34
127.68
125.35
77.59
77.16
76.74
32.70
31.84
29.14
28.56
22.77
14.24
f1 (ppm)

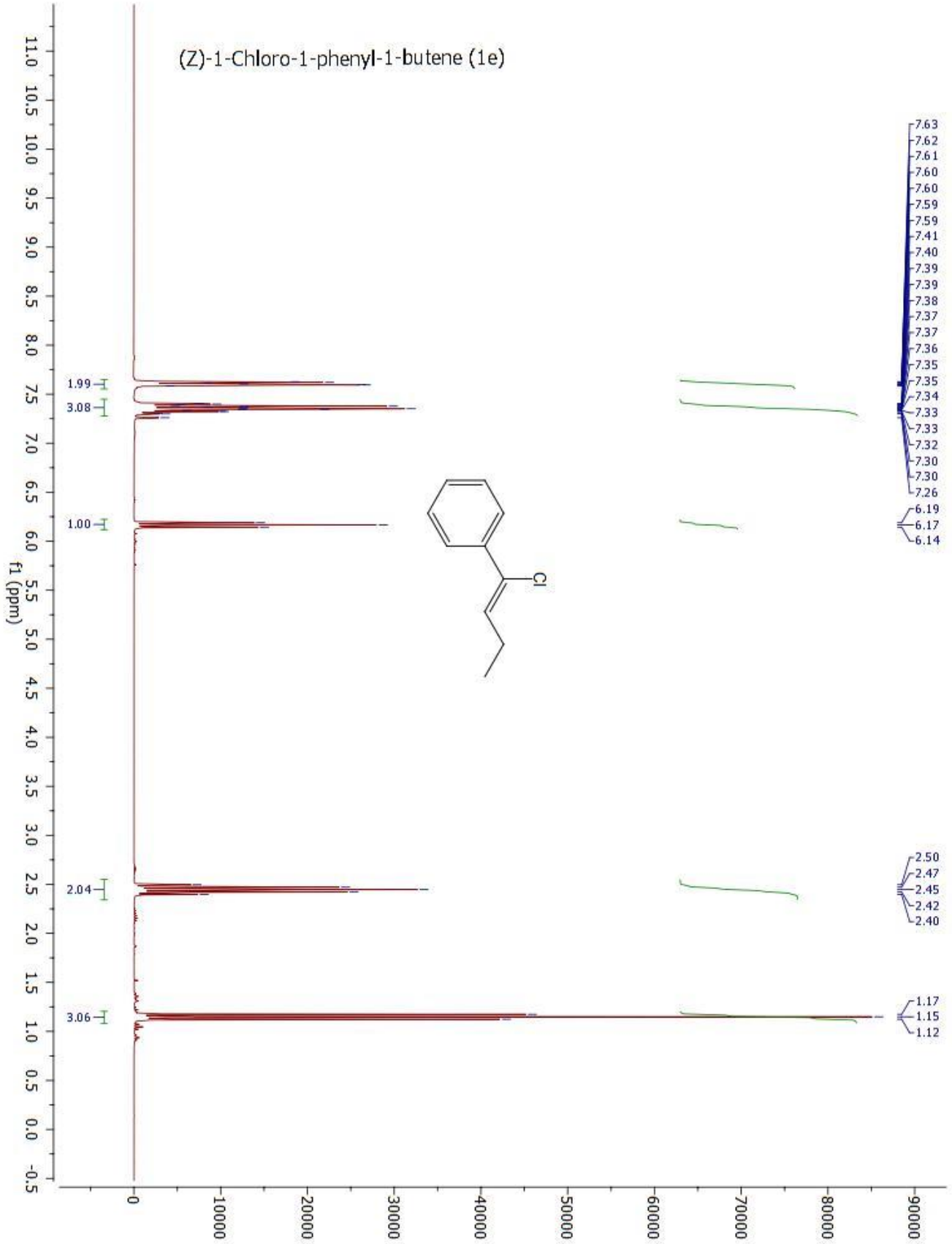

(E)-1-bromocycloheptene (1c)
f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
1.00
2.01
2.02
6.35
Br
7.26
6.22
6.20
6.18
2.70
2.68
2.66
2.11
2.08
2.07
2.05
1.77
1.76
1.51

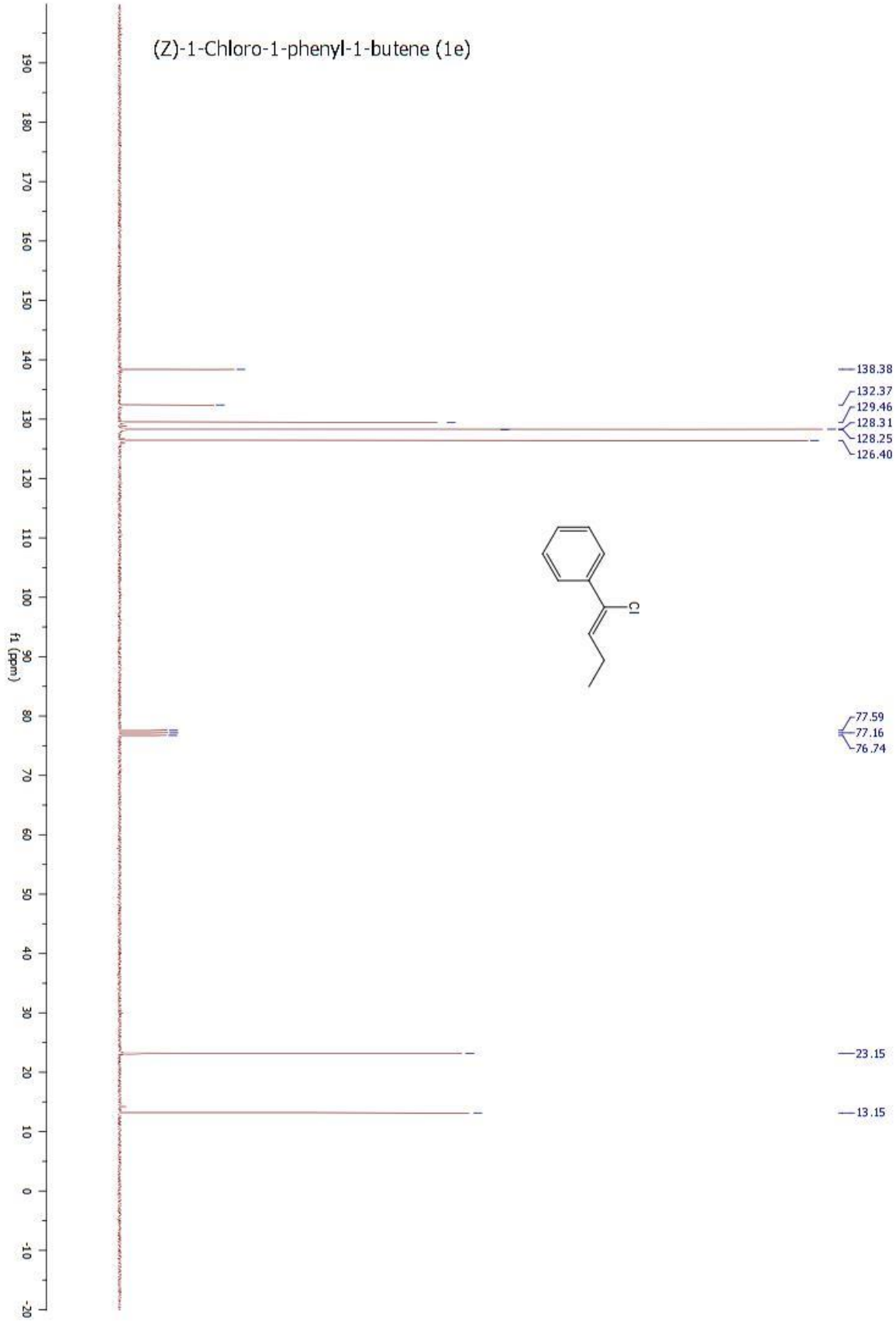

(E)-1-bromocycloheptene (1c)
Br
133.52
126.29
77.58
77.16
76.74
40.79
30.77
29.35
26.54
26.38
f1 (ppm)

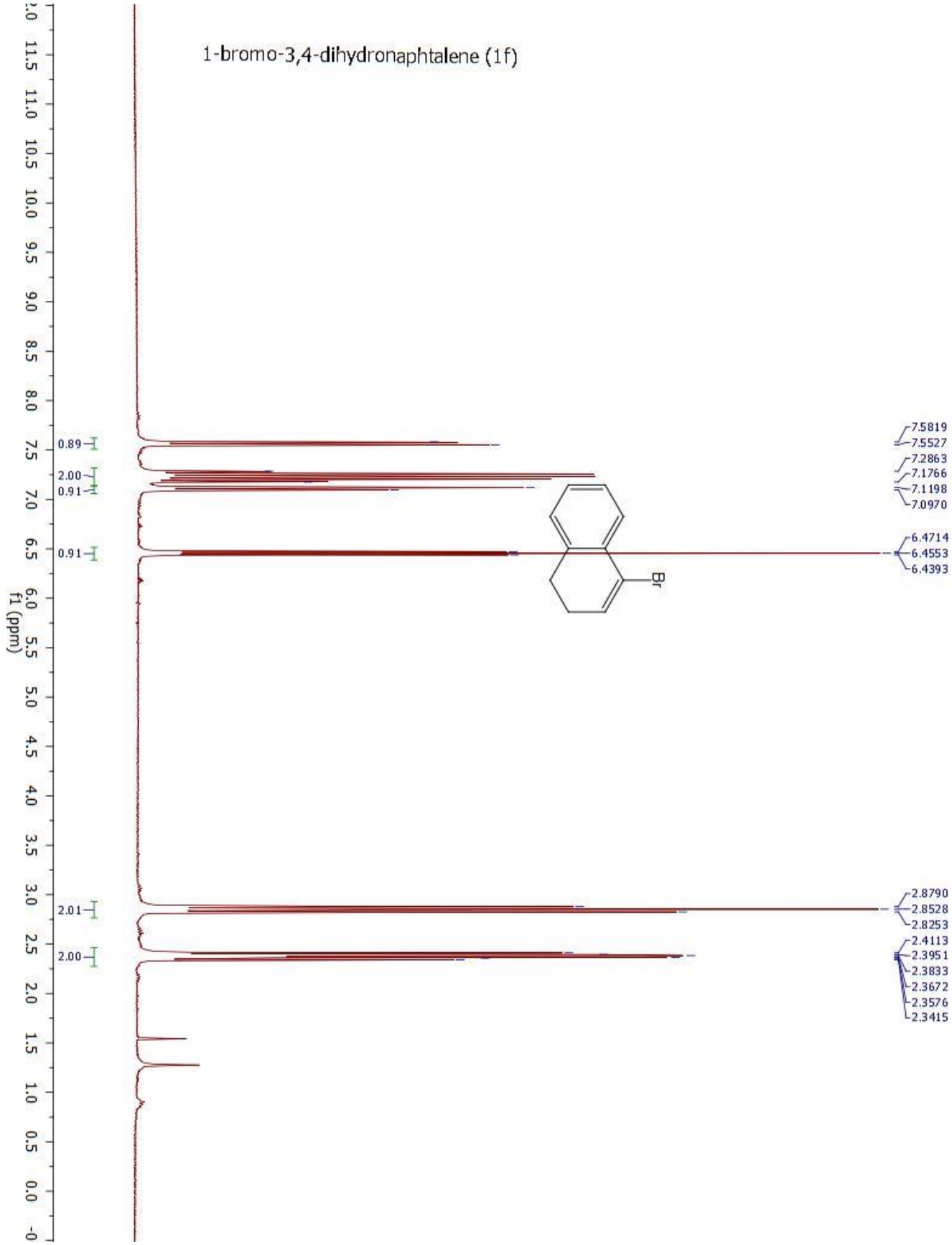

(Z)-(1-Chloro-1-propenyl)benzene (1d)
f1 (ppm)
2.00
3.27
0.97
0.03
2.97
0.10
7.59
7.54
7.40
7.28
7.26
7.26
6.24
6.22
6.20
6.18
6.08
6.06
6.03
6.01
1.97
1.95
1.75
1.73
Cl

(Z)-(1-Chloro-1-propenyl)benzene (1d)

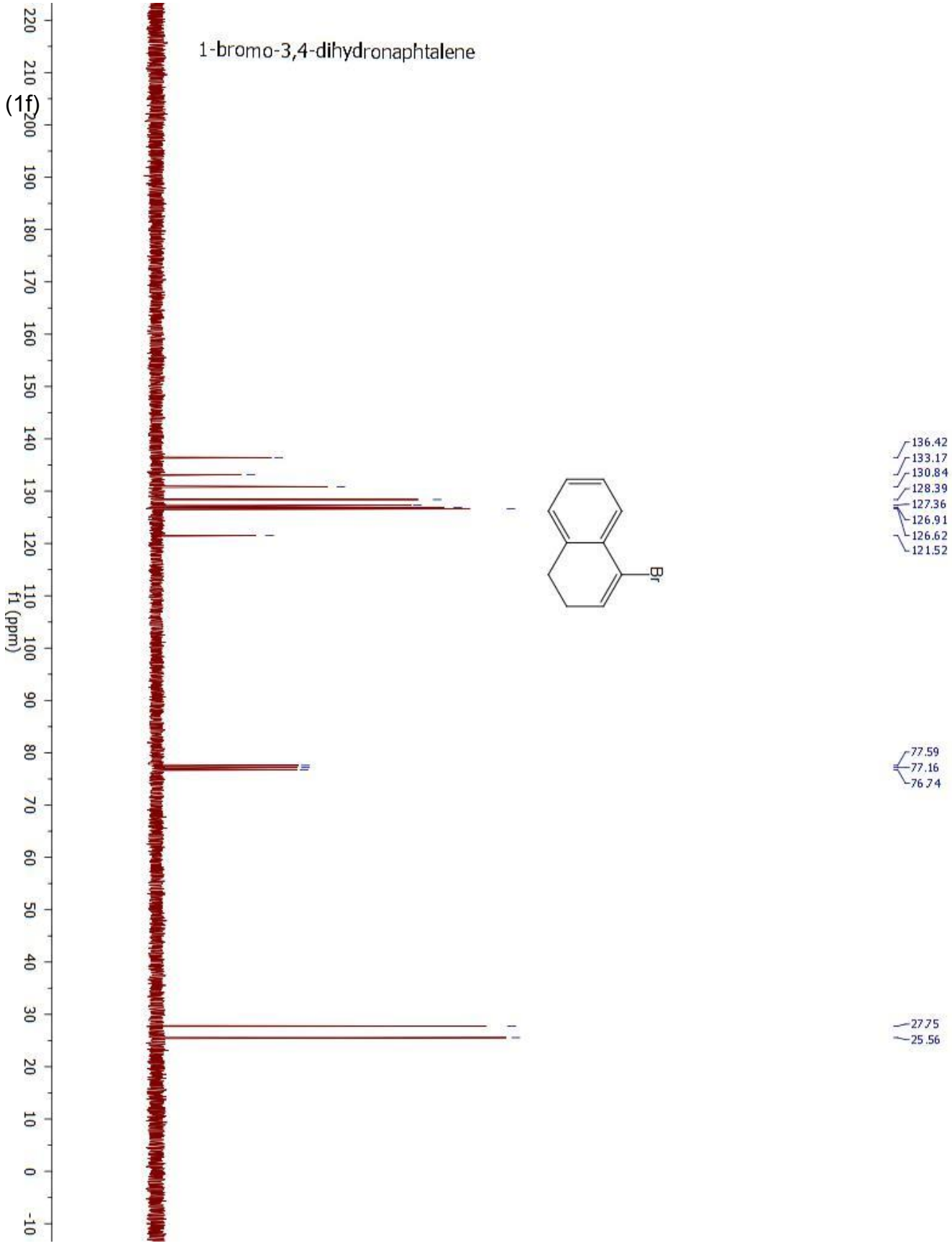


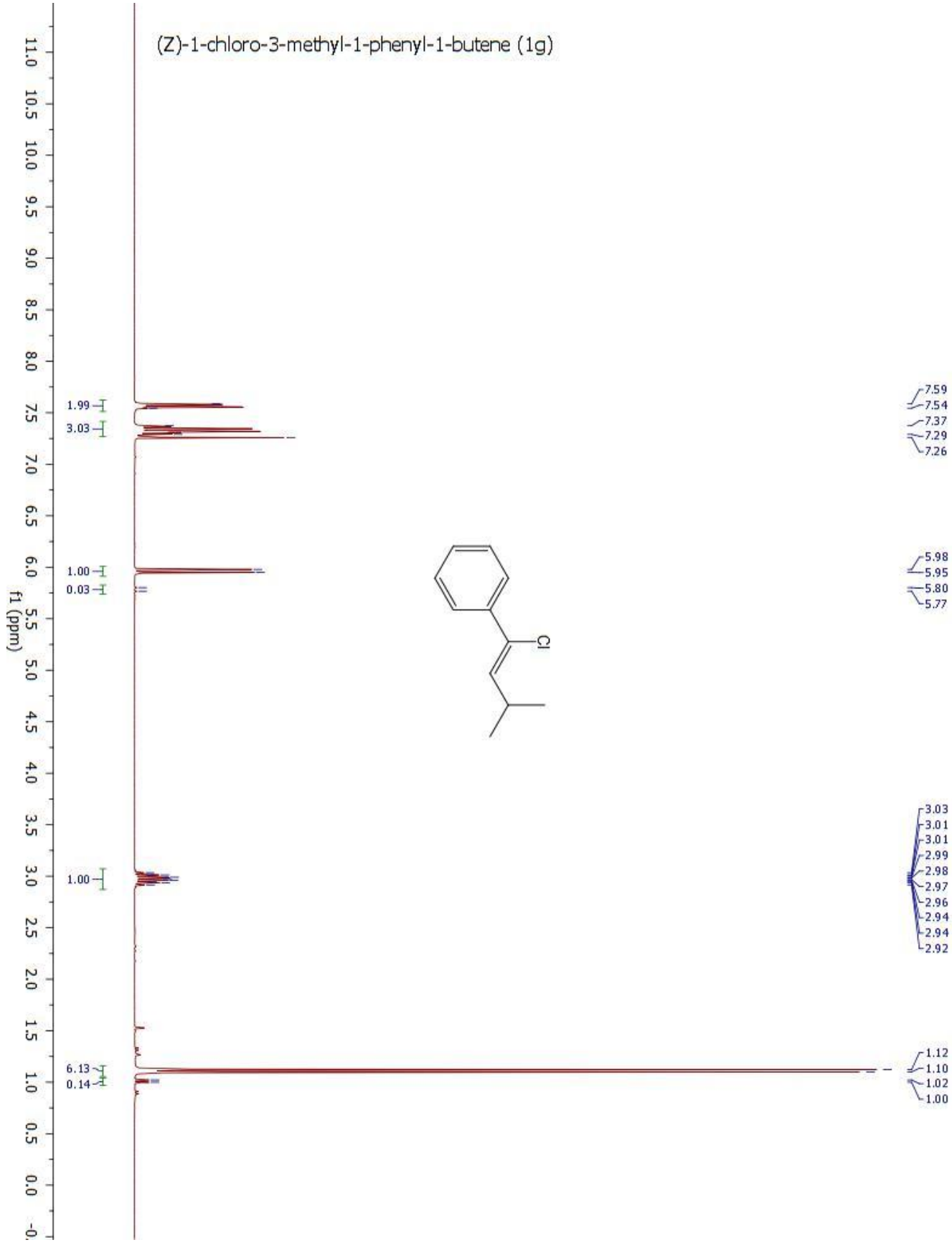

(Z)-1-Chloro-1-phenyl-1-butene (1e)
Cl
f1 (ppm)
1.99
3.08
1.00
2.04
3.06
7.63
7.62
7.61
7.60
7.60
7.59
7.59
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.30
7.30
7.26
6.19
6.17
6.14
2.50
2.47
2.45
2.42
2.40
1.17
1.15
1.12

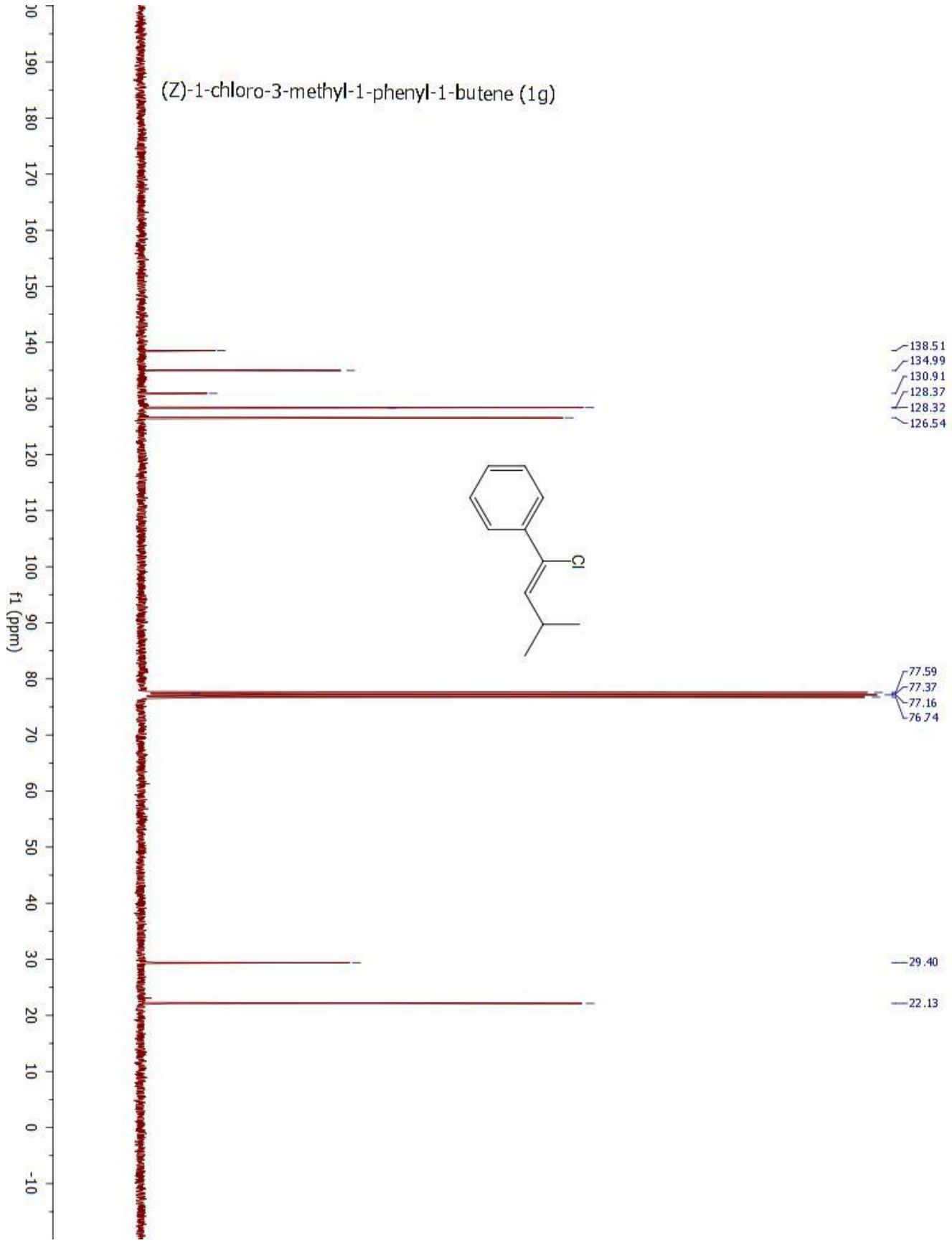

(Z)-1-Chloro-1-phenyl-1-butene (1e)
138.38
132.37
129.46
128.31
128.25
126.40
77.59
77.16
76.74
23.15
13.15
Cl
f1 (ppm)

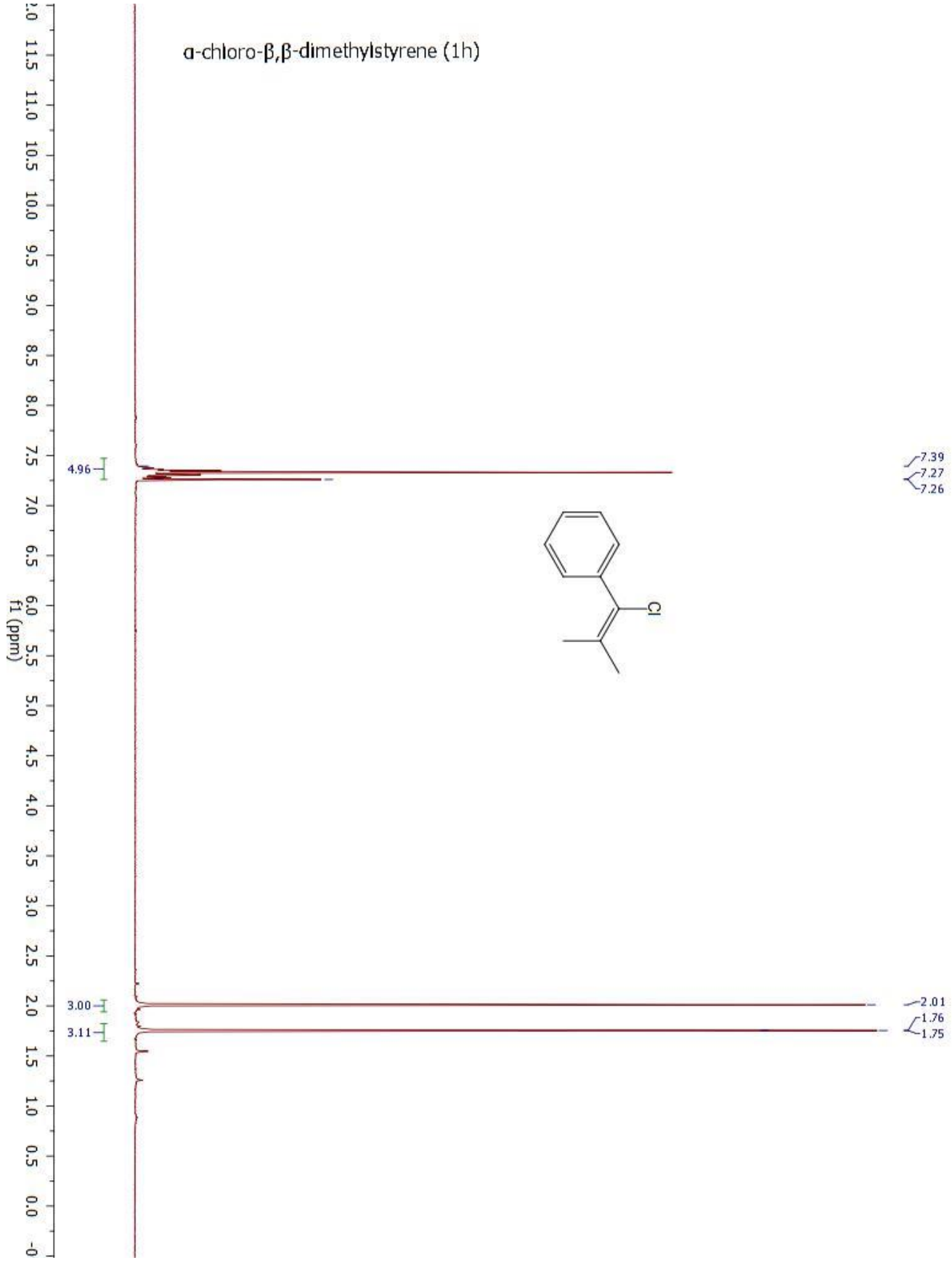

1-bromo-3,4-dihydronaphtalene (1f)
f1 (ppm)
0.89
2.00
0.91
0.91
2.01
2.00
7.5819
7.5527
7.2863
7.1766
7.1198
7.0970
6.4714
6.4553
6.4393
2.8790
2.8528
2.8253
2.4113
2.3951
2.3833
2.3672
2.3576
2.3415
Br

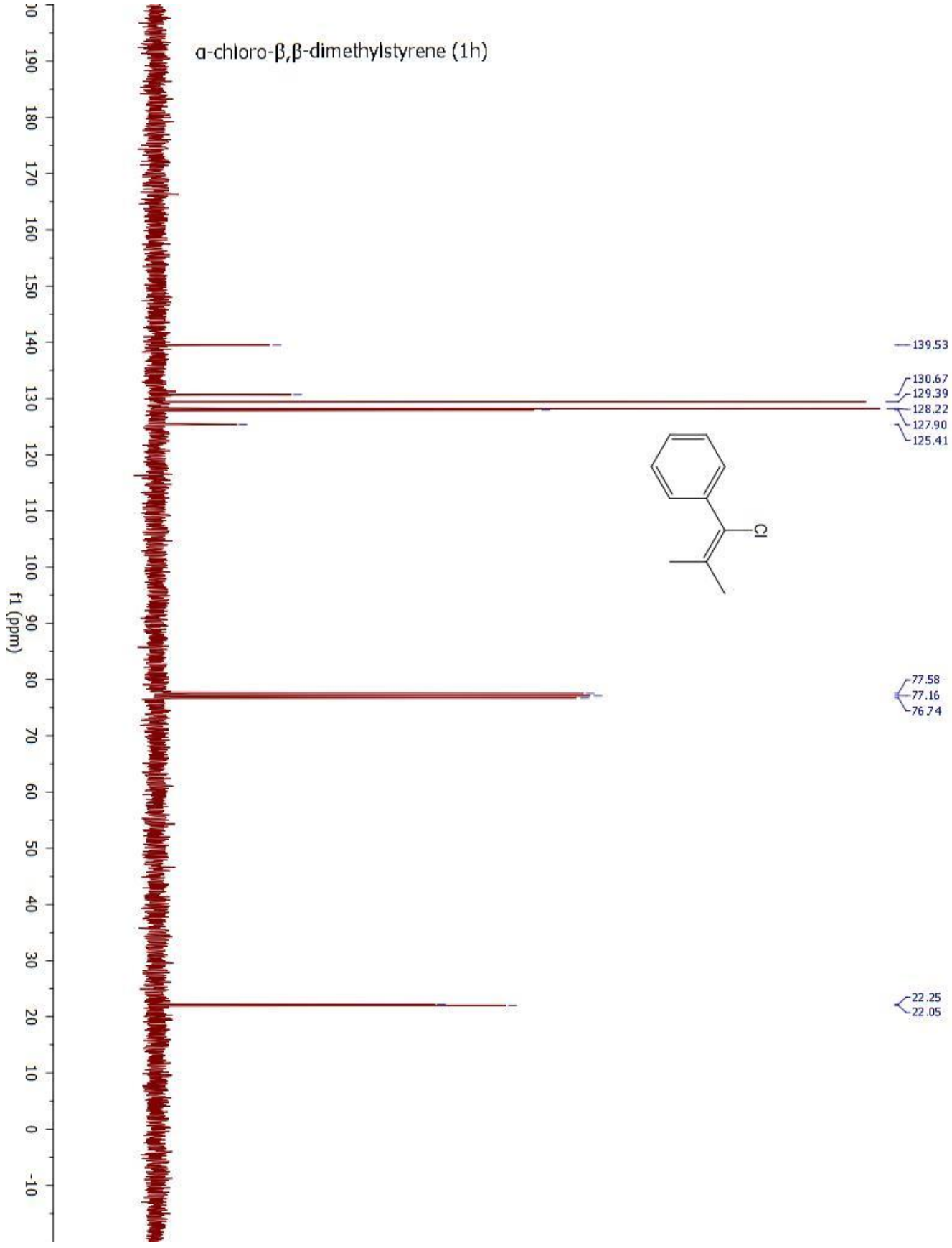
(1f)

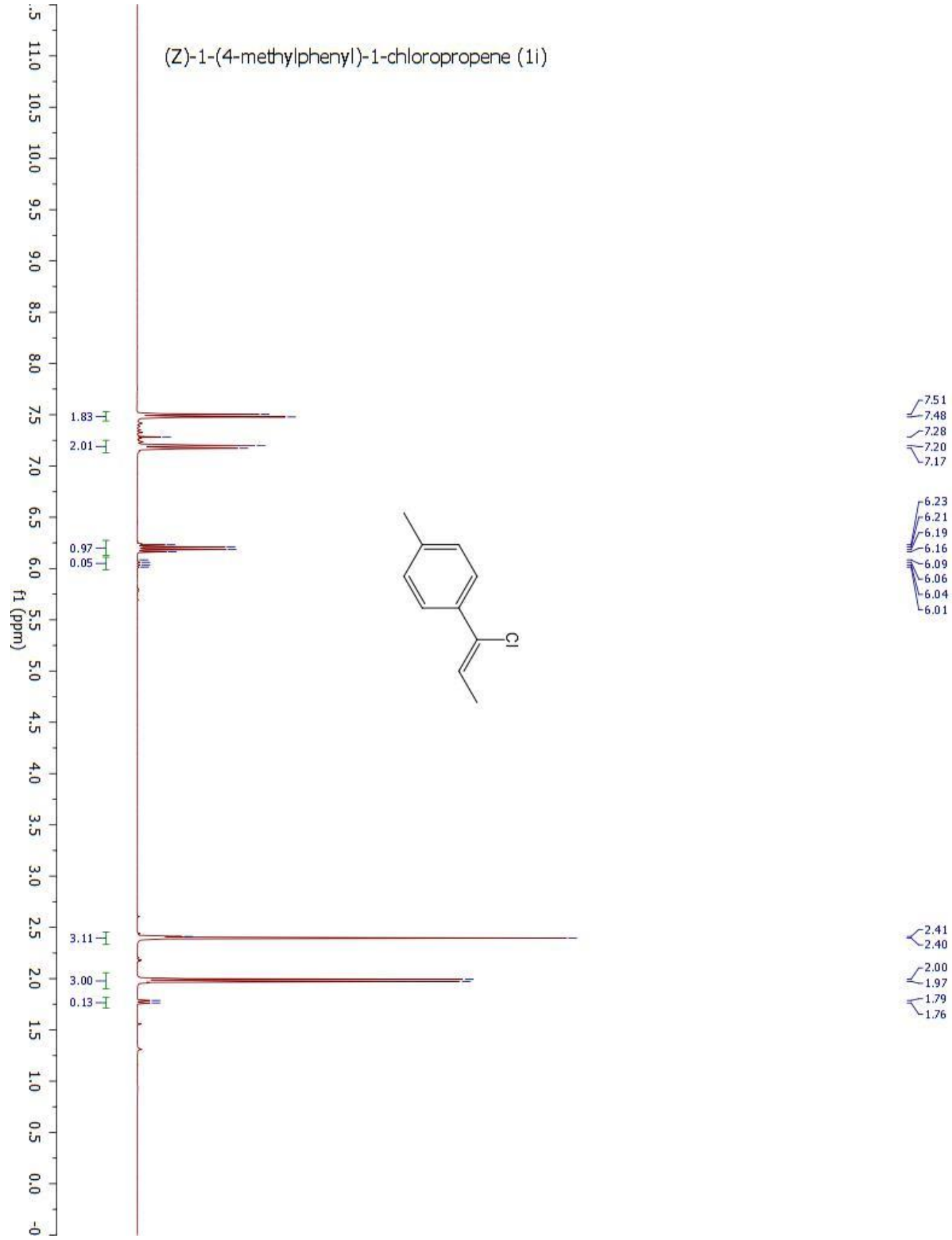

1-bromo-3,4-dihydronaphtalene
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Br
136.42
133.17
130.84
128.39
127.36
126.91
126.62
121.52
77.59
77.16
76.74
27.75
25.56


(Z)-1-chloro-3-methyl-1-phenyl-1-butene (1g)
f1 (ppm)
1.99
3.03
1.00
0.03
1.00
6.13
0.14
7.59
7.54
7.37
7.29
7.26
5.98
5.95
5.80
5.77
3.03
3.01
3.01
2.99
2.98
2.97
2.96
2.94
2.94
2.92
1.12
1.10
1.02
1.00
Cl

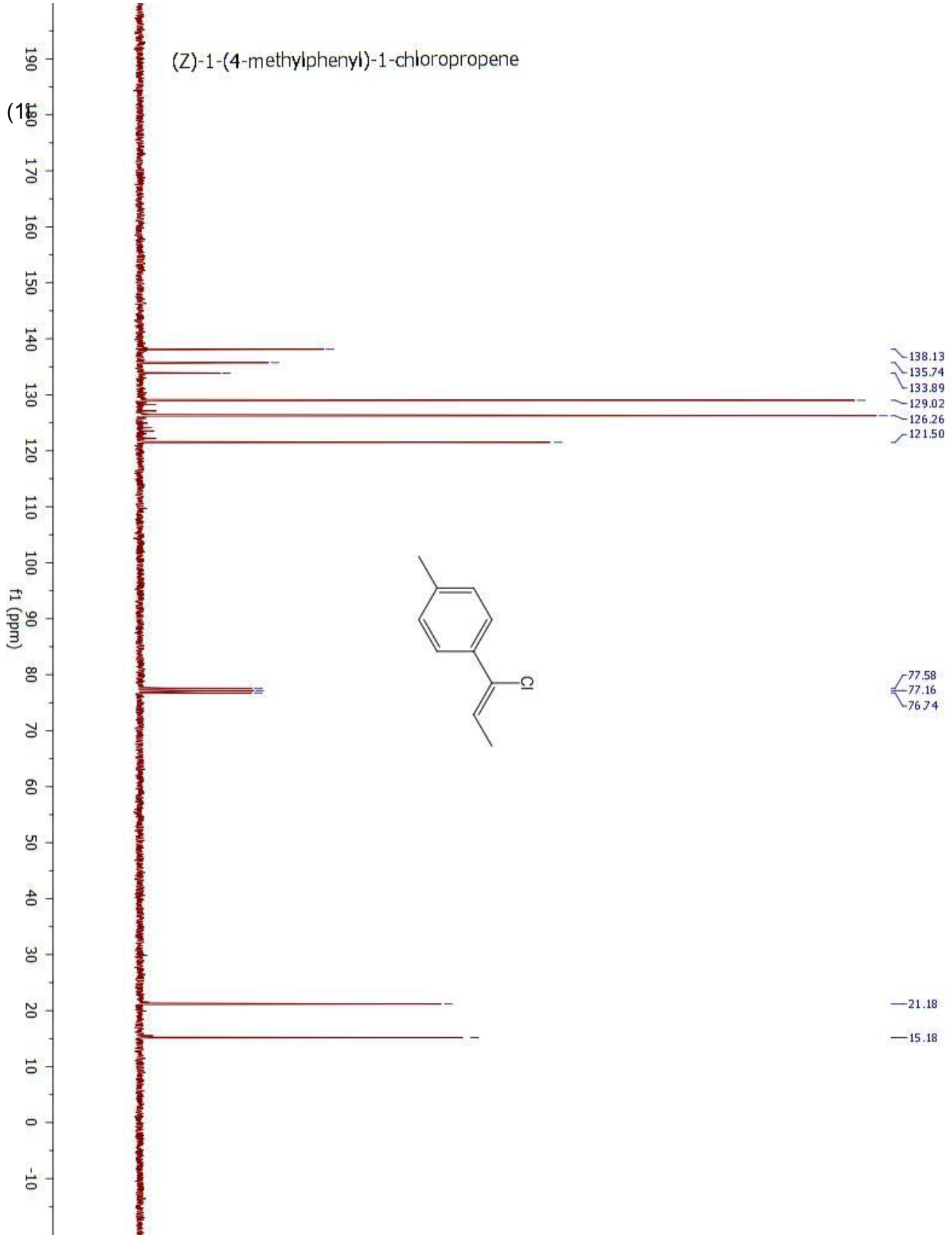

(Z)-1-chloro-3-methyl-1-phenyl-1-butene (1g)
Cl
138.51
134.99
130.91
128.37
128.32
126.54
77.59
77.37
77.16
76.74
29.40
22.13
f1 (ppm)

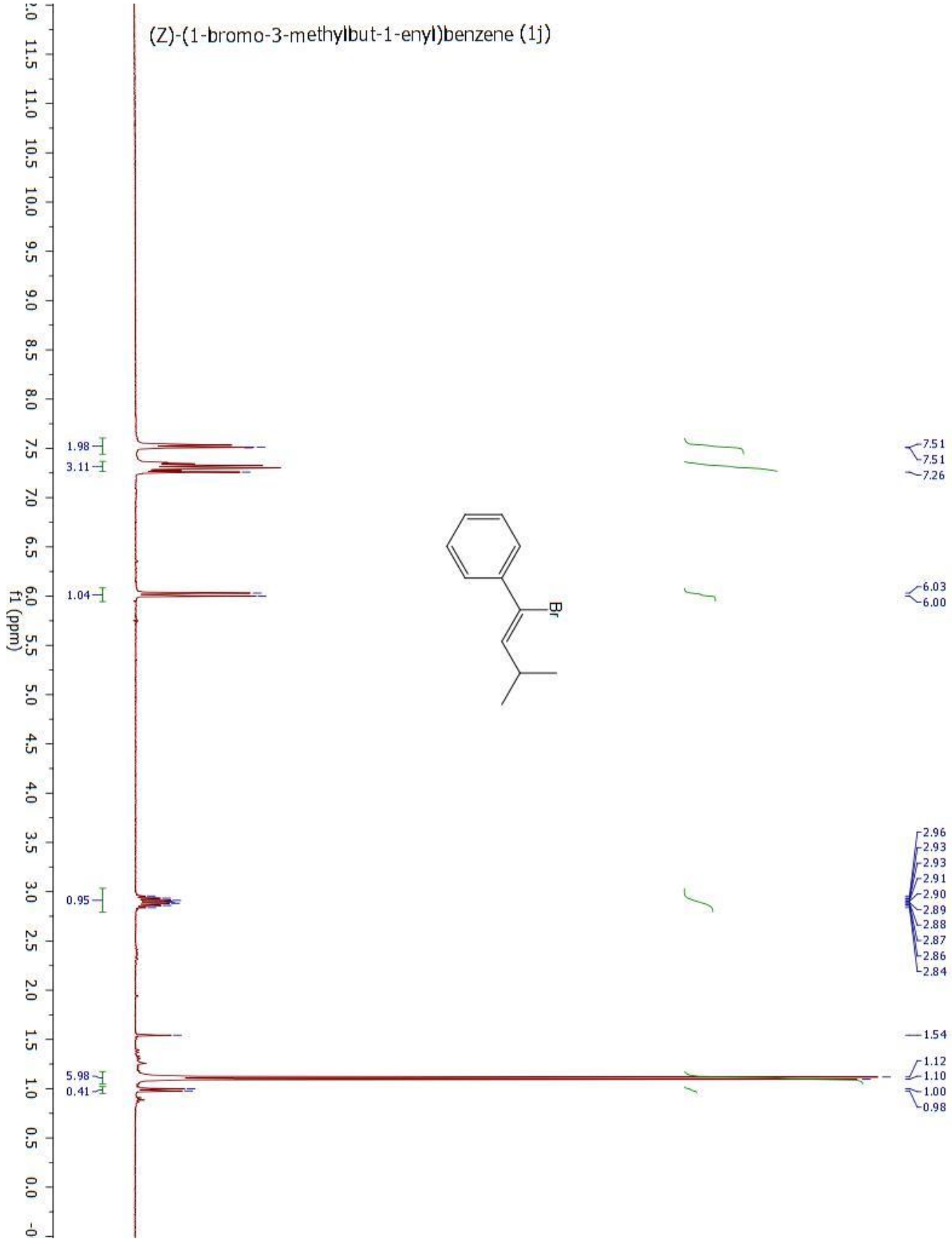

α-chloro-β,β-dimethylstyrene (1h)
f1 (ppm)
4.96
3.00
3.11
7.39
7.27
7.26
2.01
1.76
1.75
Cl

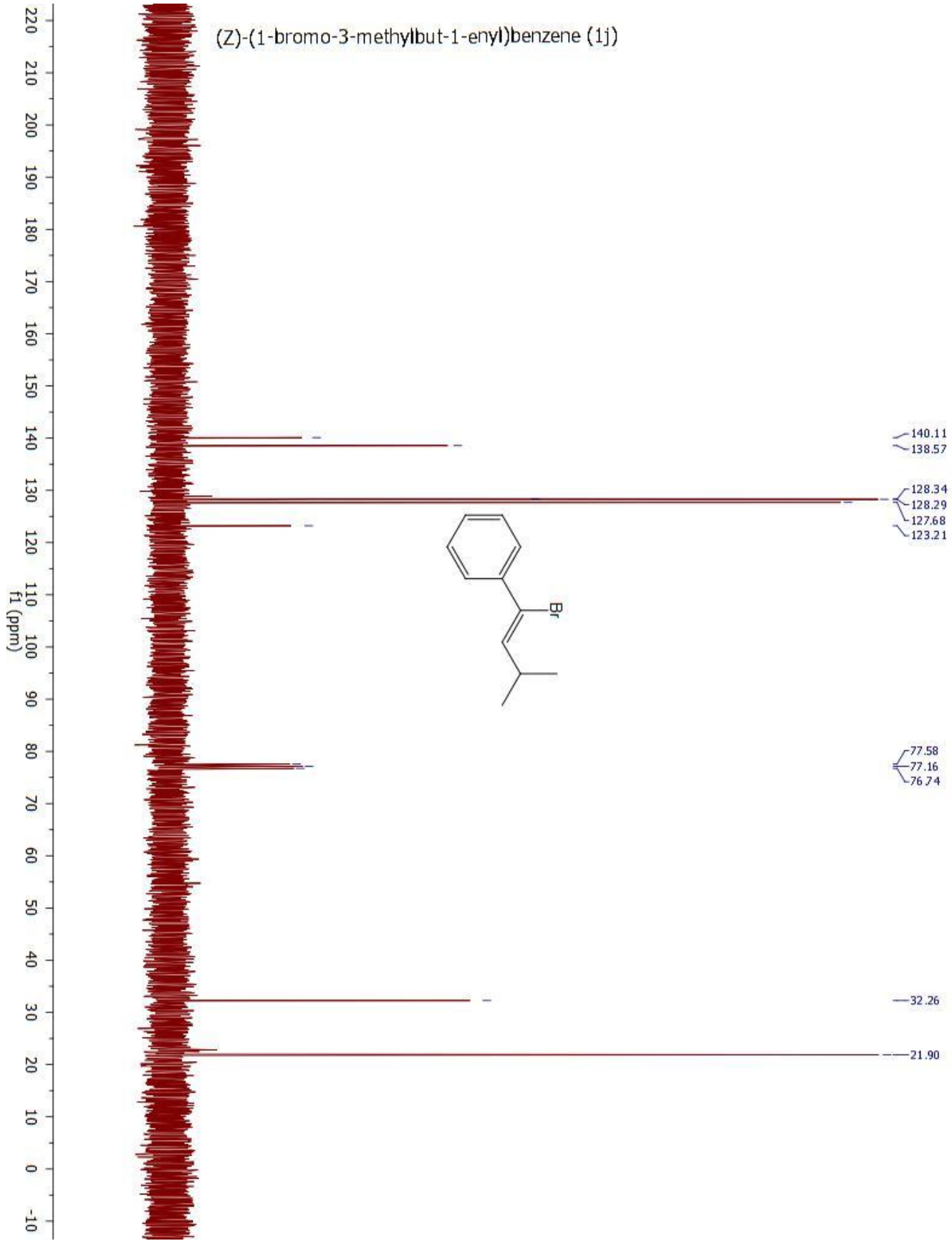

α-chloro-β,β-dimethylstyrene (1h)
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
139.53
130.67
129.39
128.22
127.90
125.41
Cl
77.58
77.16
76.74
22.25
22.05

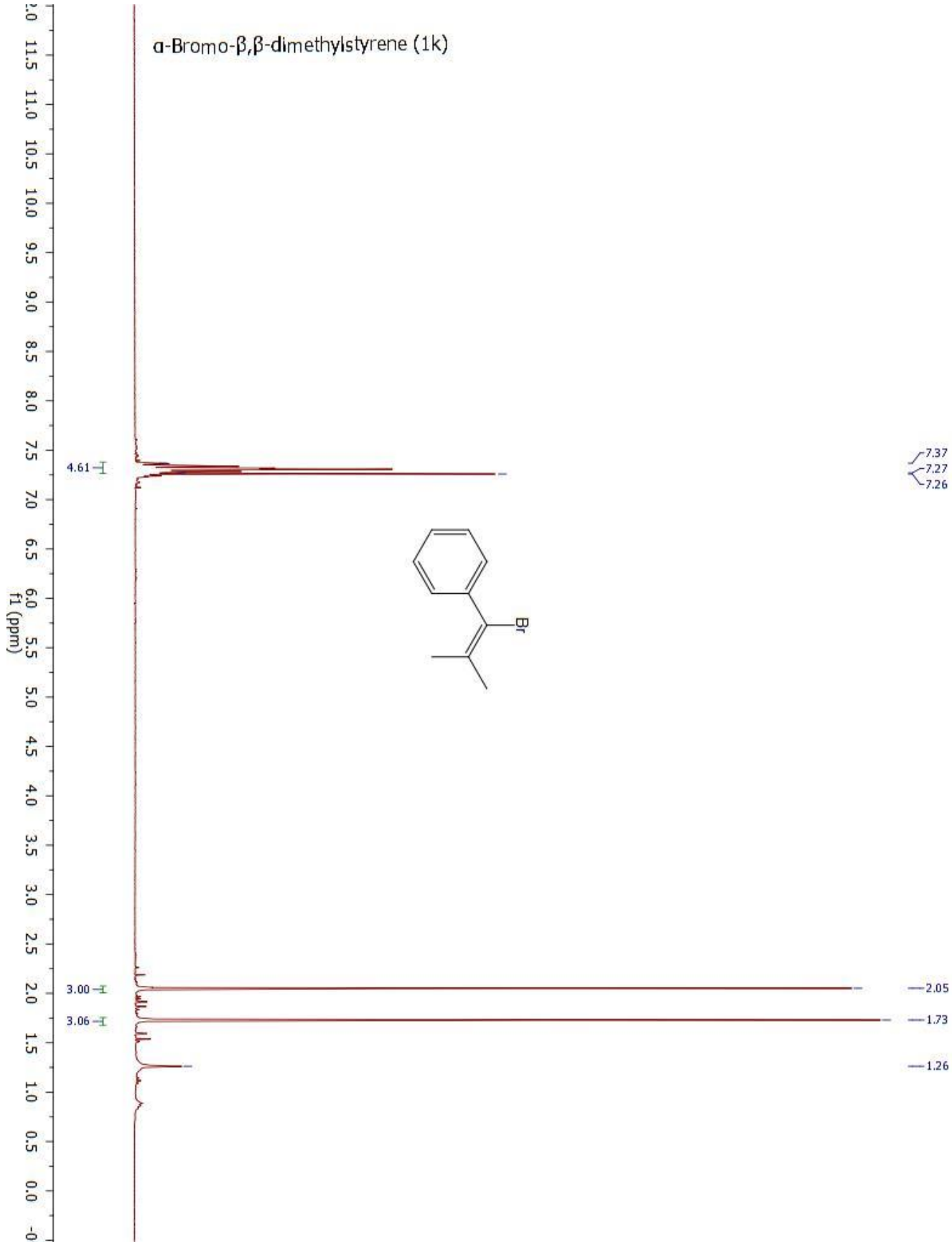

(Z)-1-(4-methylphenyl)-1-chloropropene (1i)
Cl
f1 (ppm)
1.83
2.01
0.97
0.05
3.11
3.00
0.13
7.51
7.48
7.28
7.20
7.17
6.23
6.21
6.19
6.16
6.09
6.06
6.04
6.01
2.41
2.40
2.00
1.97
1.79
1.76

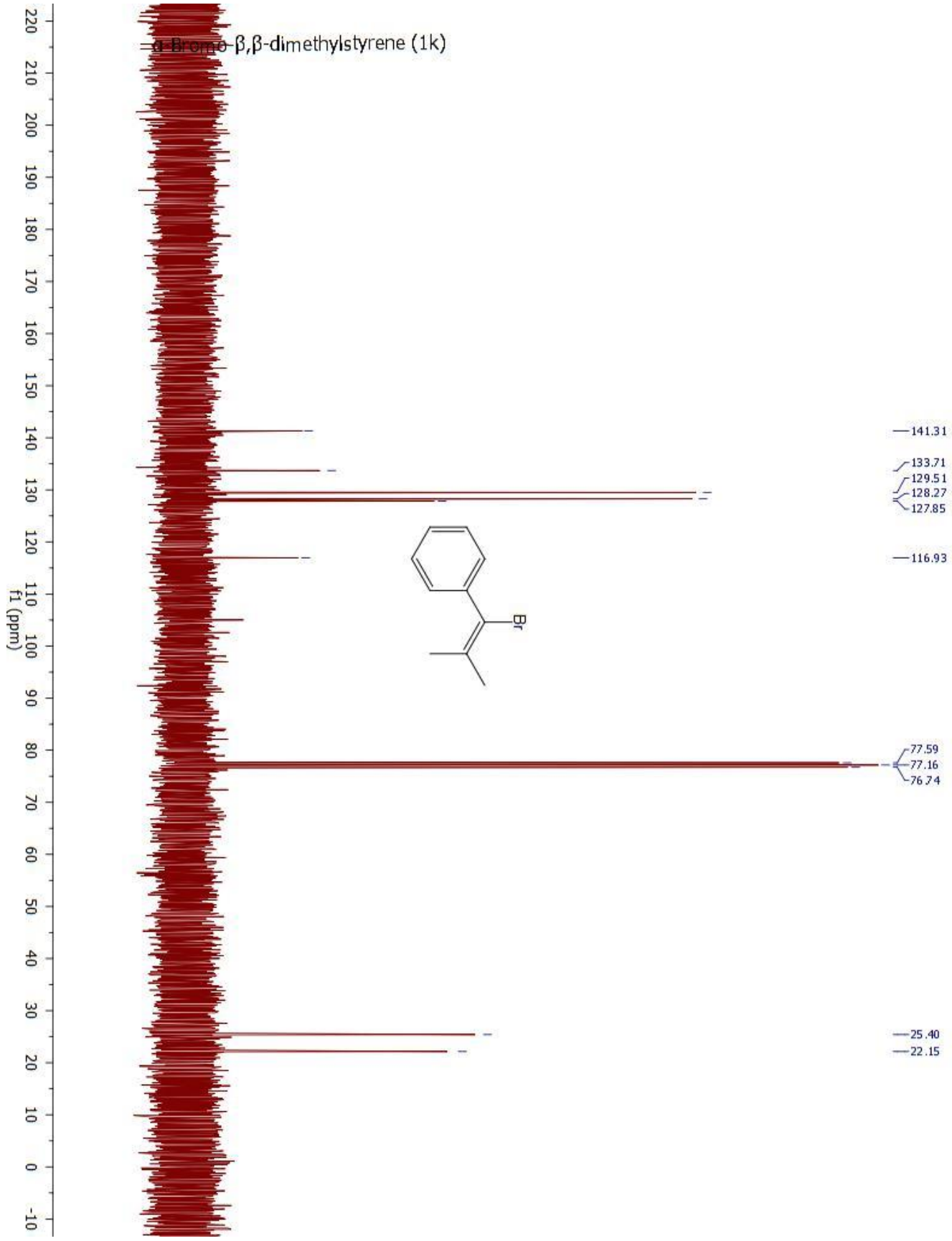
(1

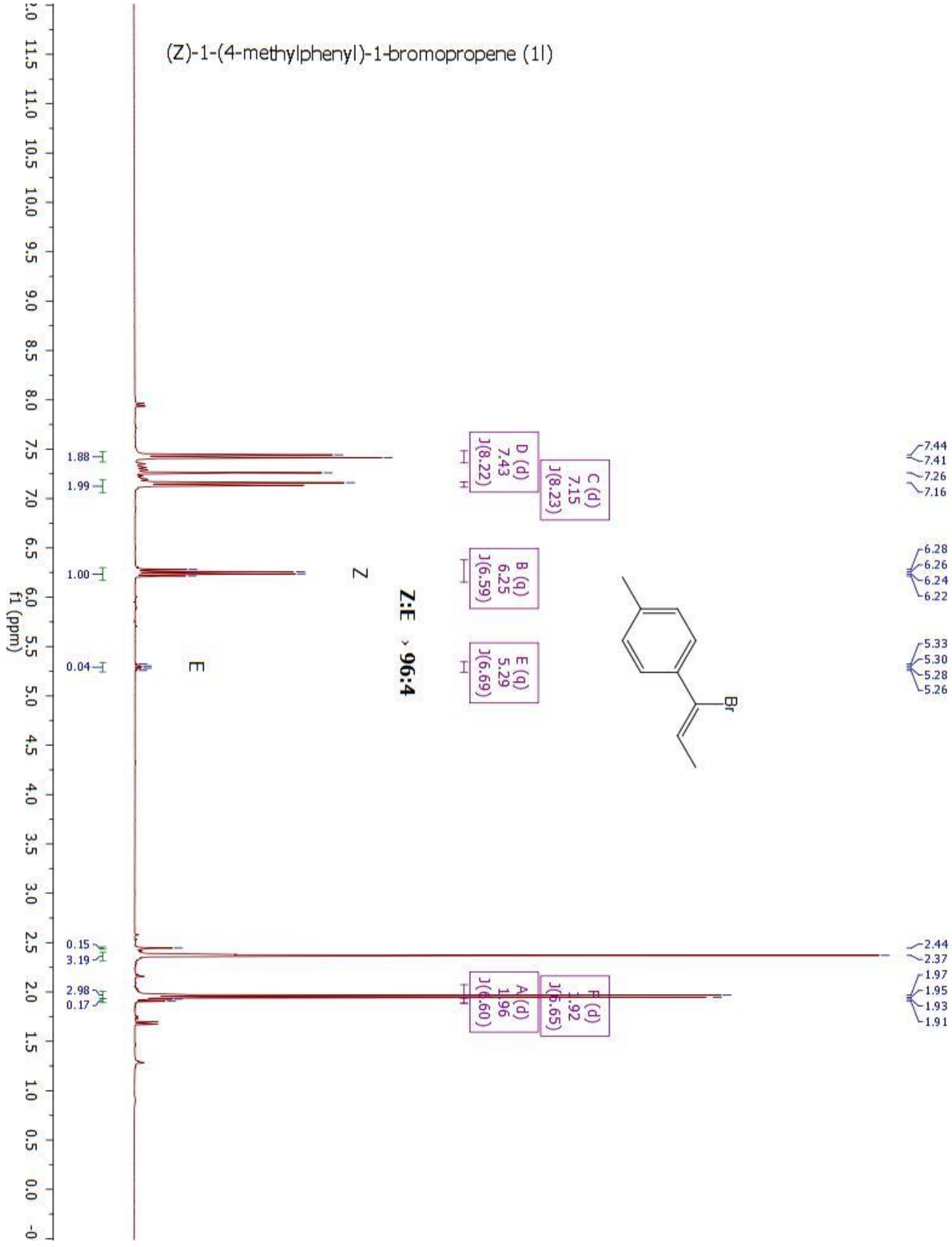

(Z)-1-(4-methylphenyl)-1-chloropropene
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
138.13
135.74
133.89
129.02
126.26
121.50
77.58
77.16
76.74
21.18
15.18
Cl

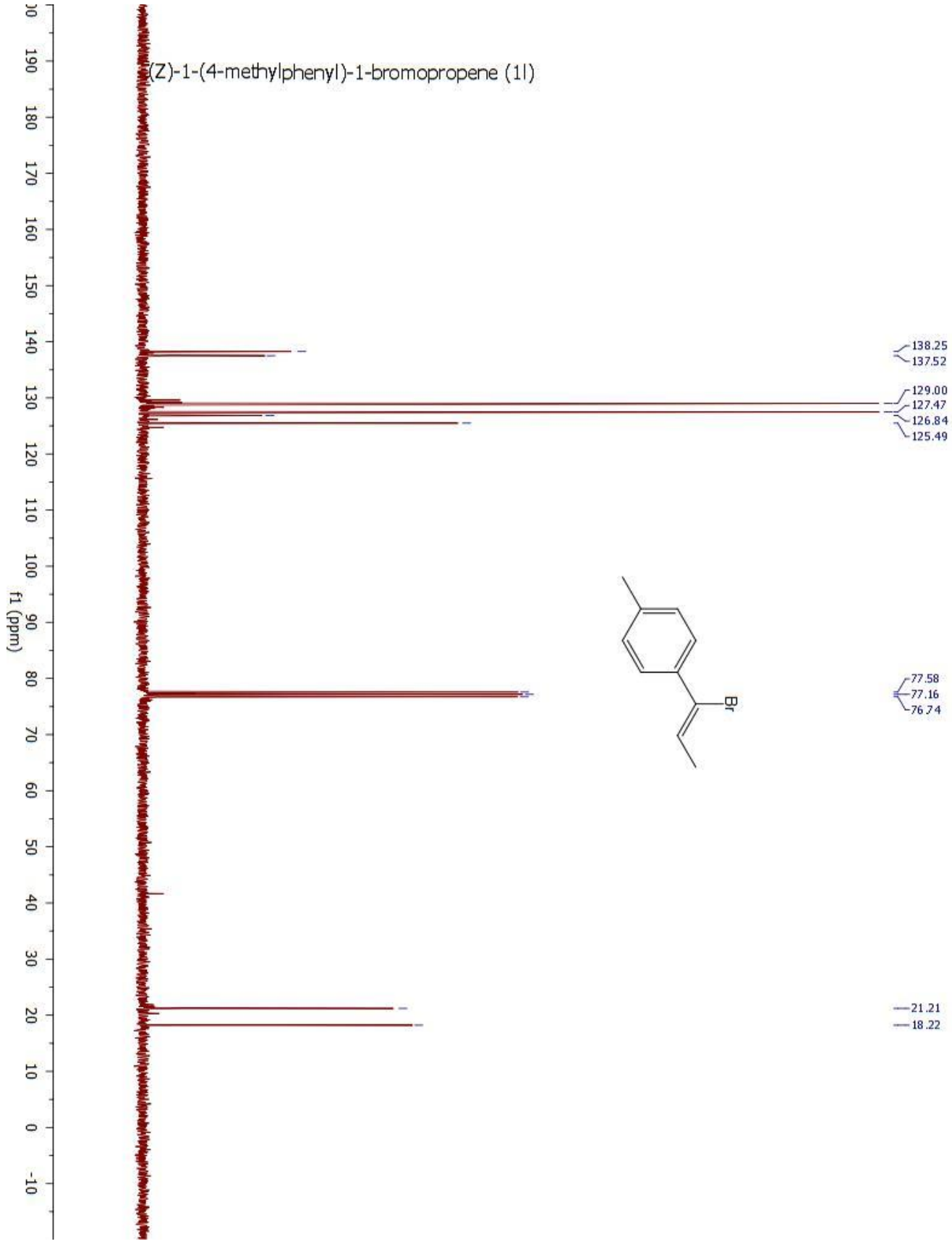

(Z)-(1-bromo-3-methylbut-1-enyl)benzene (1j)
Br
1.98
3.11
1.04
0.95
5.98
0.41
7.51
7.51
7.26
6.03
6.00
2.96
2.93
2.93
2.91
2.90
2.89
2.88
2.87
2.86
2.84
1.54
1.12
1.10
1.00
0.98
f1 (ppm)

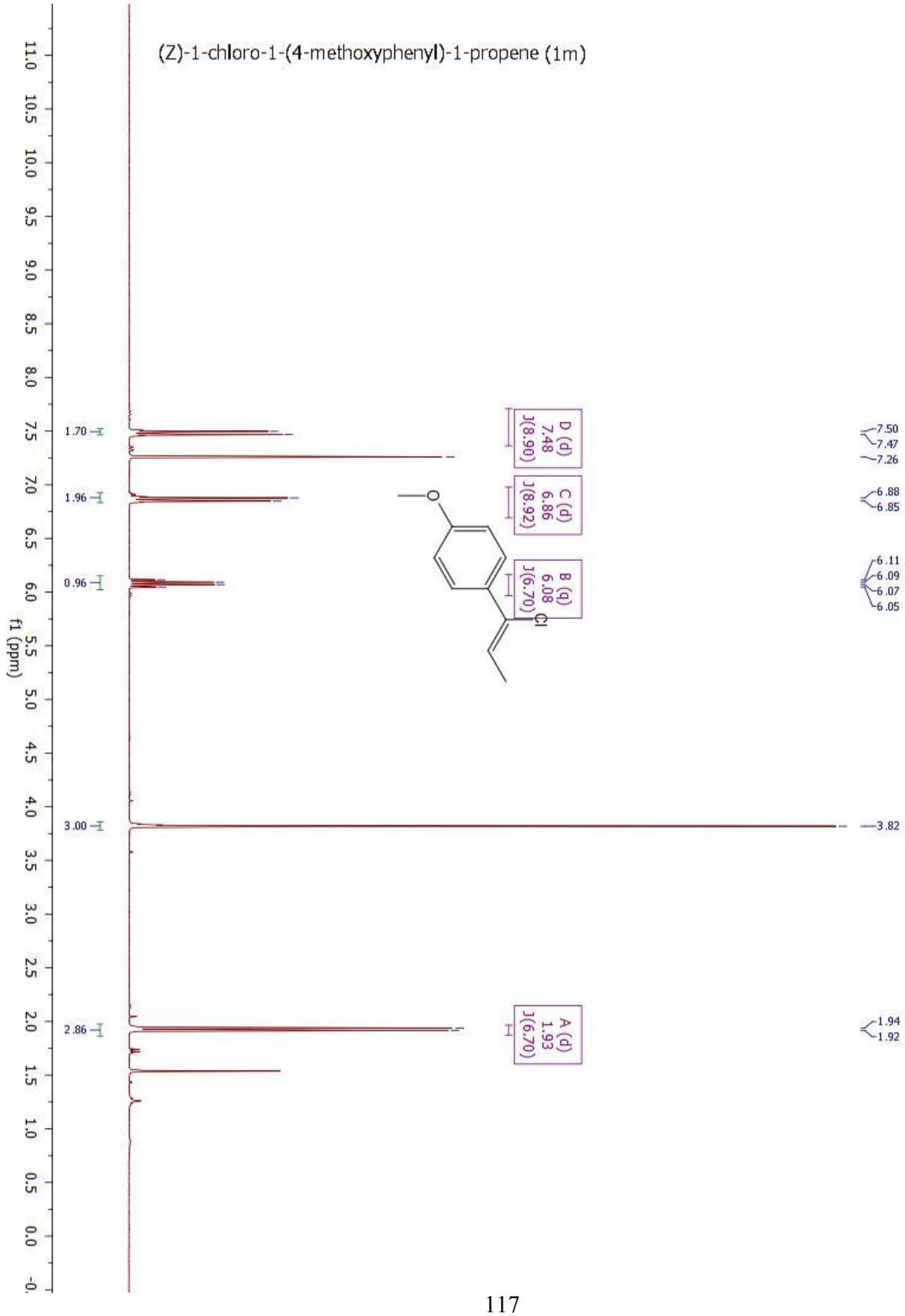

(Z)-(1-bromo-3-methylbut-1-enyl)benzene (1j)
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
140.11
138.57
128.34
128.29
127.68
123.21
Br
77.58
77.16
76.74
32.26
21.90

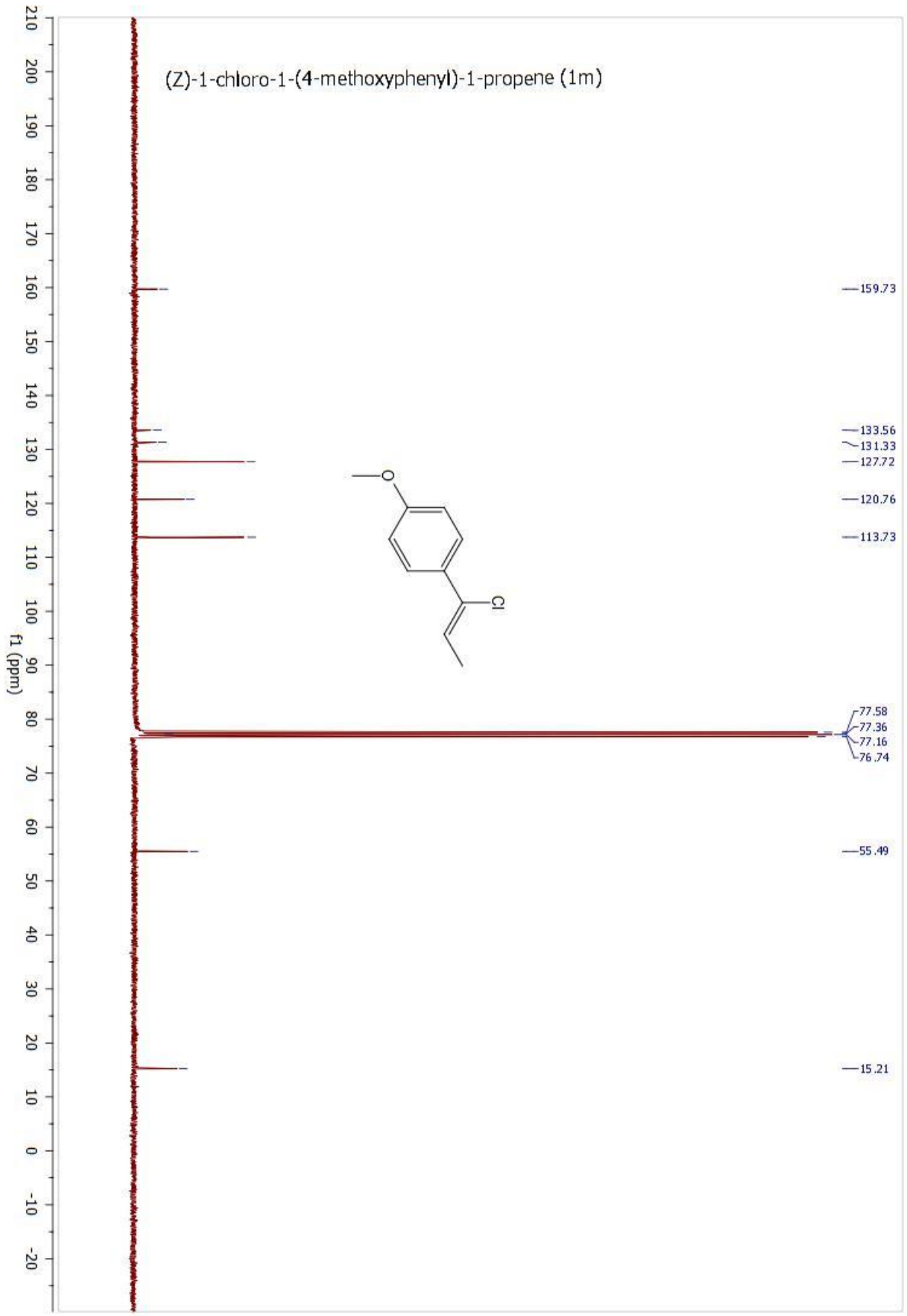

α-Bromo-β,β-dimethylstyrene (1k)
4.61
3.00
3.06
7.37
7.27
7.26
2.05
1.73
1.26
Br
f1 (ppm)

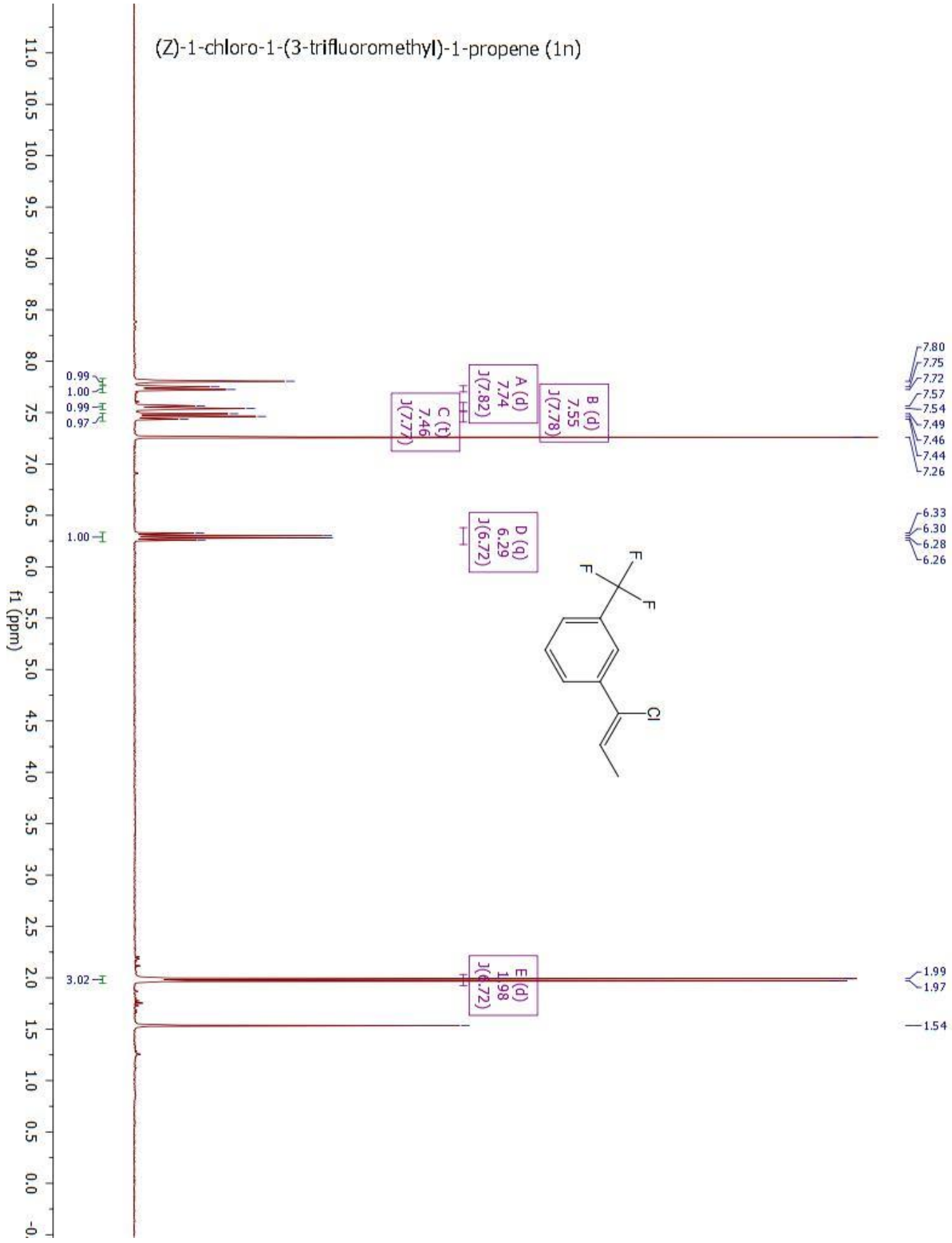

α-Bromo-β,β-dimethylstyrene (1k)
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
141.31
133.71
129.51
128.27
127.85
116.93
77.59
77.16
76.74
25.40
22.15
Br

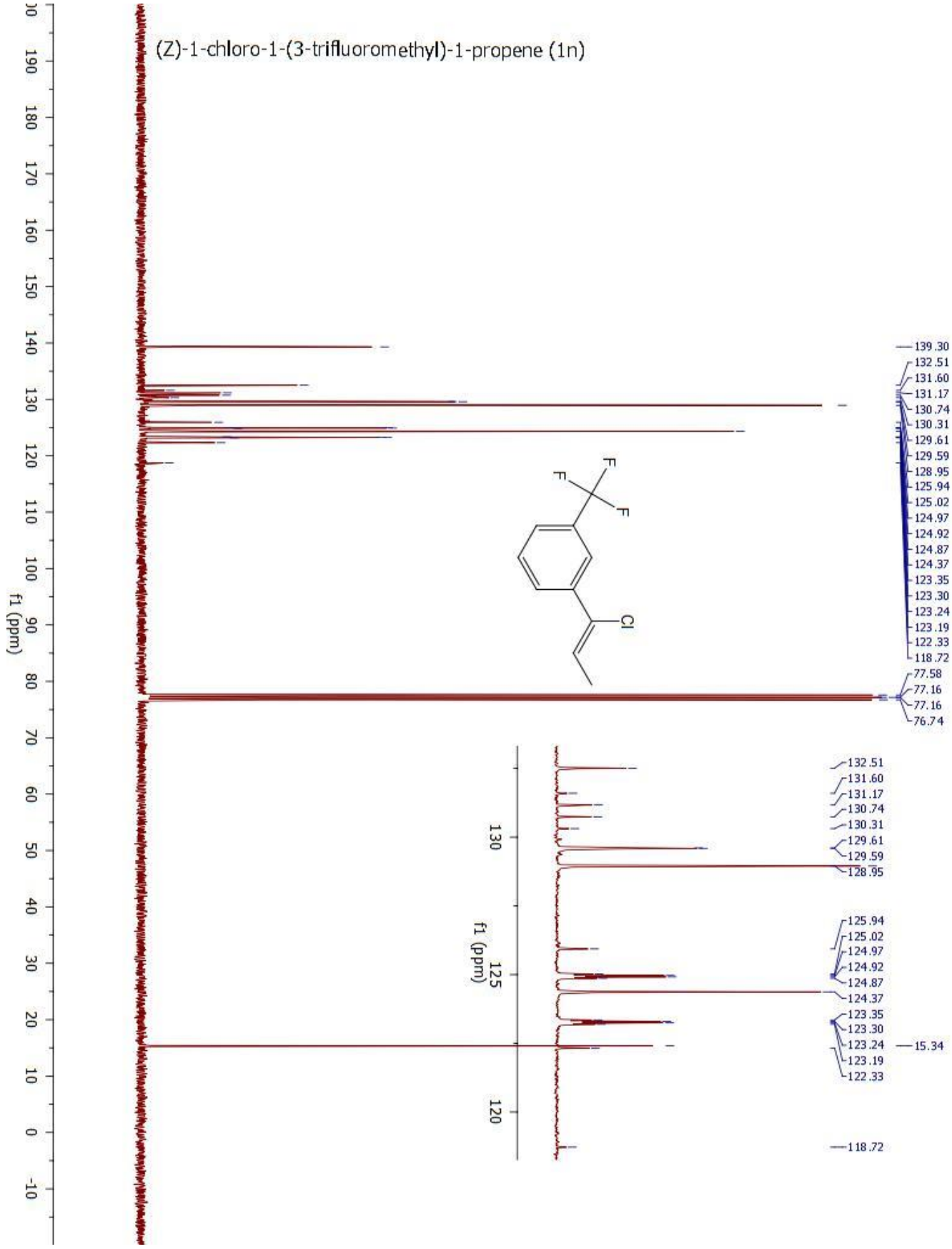

(Z)-1-(4-methylphenyl)-1-bromopropene (1l)
Z:E › 96:4
Z
E
Br
D (d) 7.43 J(8.22)
C (d) 7.15 J(8.23)
B (q) 6.25 J(6.59)
E (q) 5.29 J(6.69)
A (d) 1.96 J(6.60)
F (d) 1.92 J(6.65)
1.88
1.99
1.00
0.04
0.15
3.19
2.98
0.17
7.44
7.41
7.26
7.16
6.28
6.26
6.24
6.22
5.33
5.30
5.28
5.26
2.44
2.37
1.97
1.95
1.93
1.91
f1 (ppm)

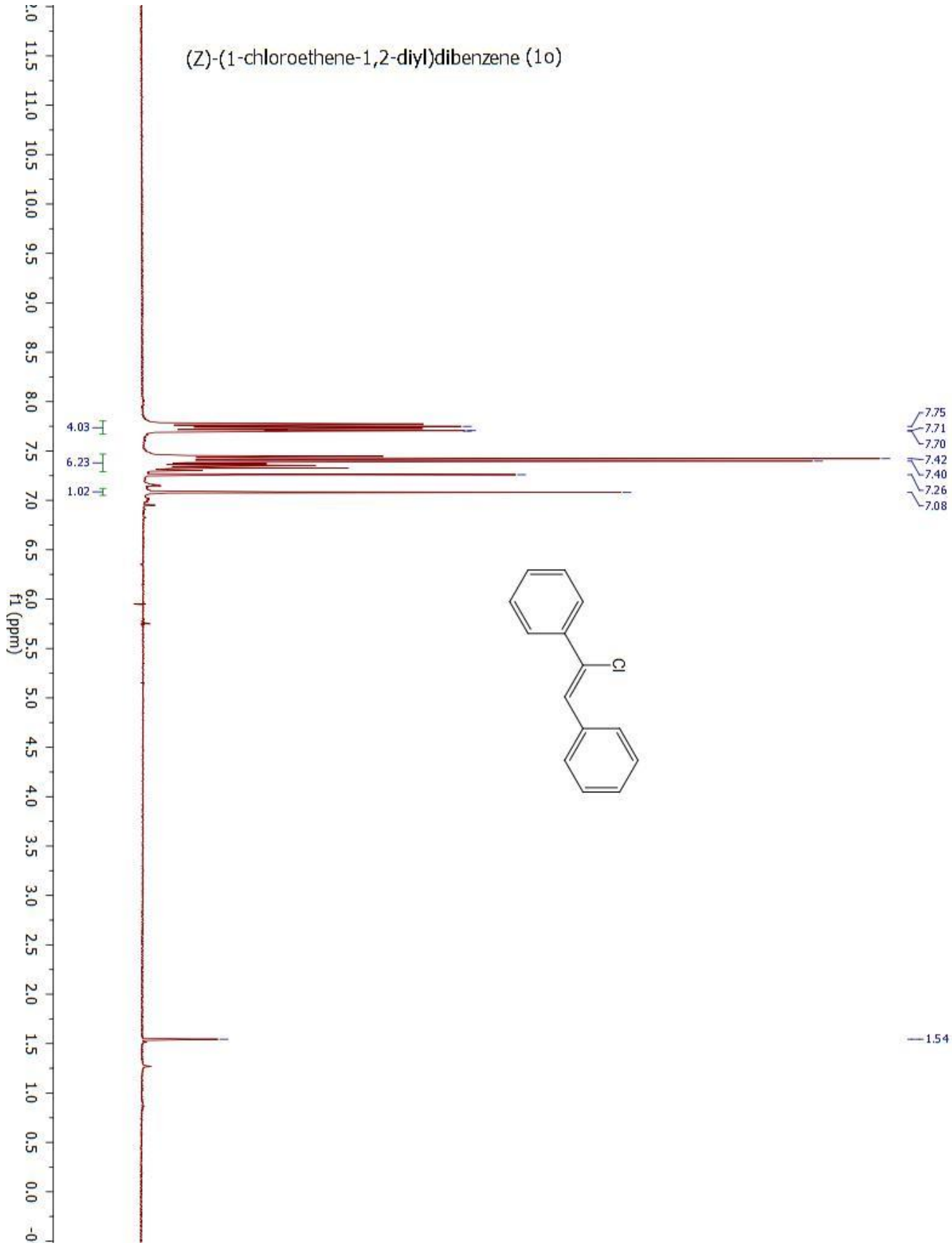

(Z)-1-(4-methylphenyl)-1-bromopropene (1l)
f1 (ppm)
138.25
137.52
129.00
127.47
126.84
125.49
77.58
77.16
76.74
21.21
18.22
Br

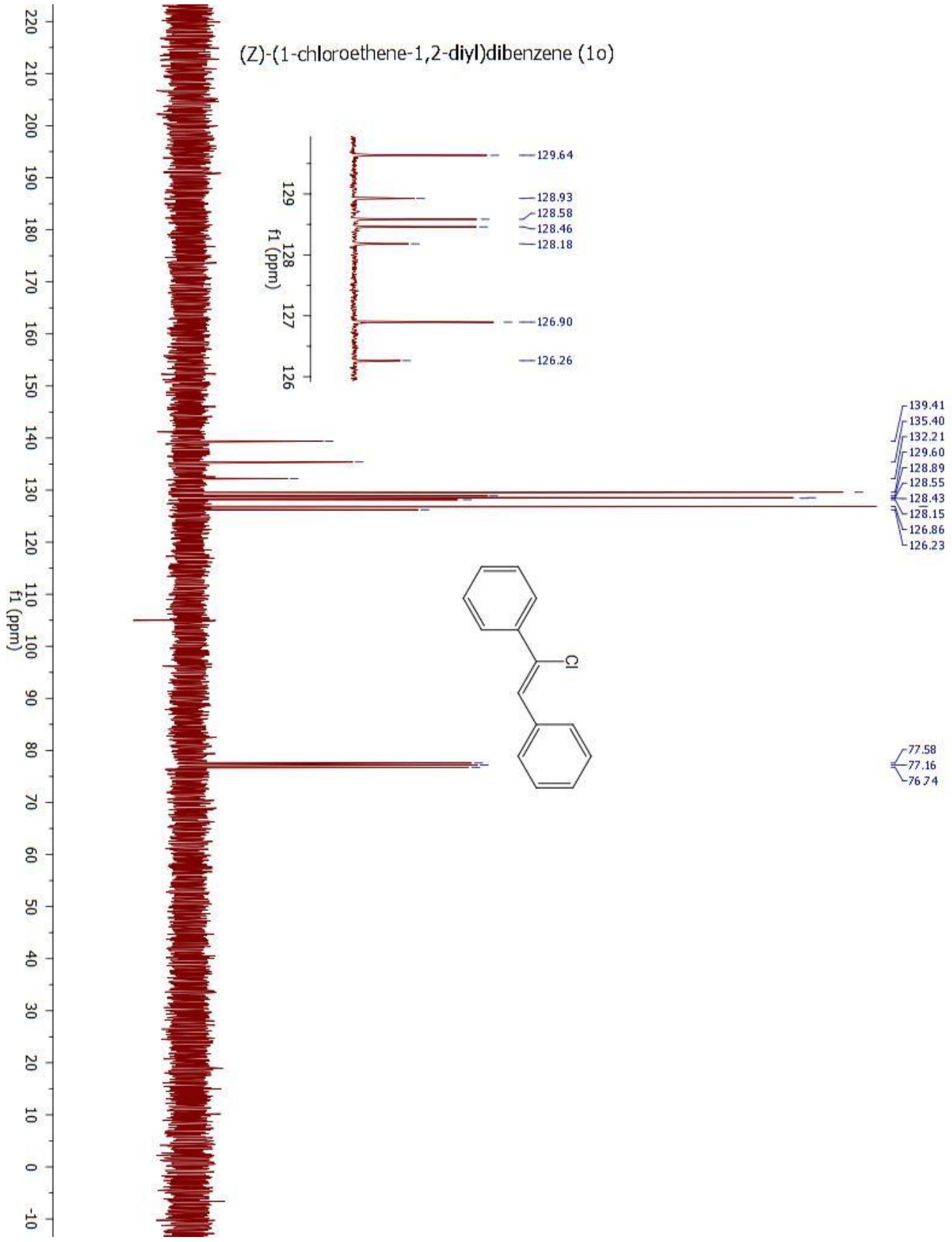

(Z)-1-chloro-1-(4-methoxyphenyl)-1-propene (1m)
D (d)
7.48
J(8.90)
C (d)
6.86
J(8.92)
B (q)
6.08
J(6.70)
A (d)
1.93
J(6.70)
Cl
1.70
1.96
0.96
3.00
2.86
7.50
7.47
7.26
6.88
6.85
6.11
6.09
6.07
6.05
3.82
1.94
1.92
f1 (ppm)

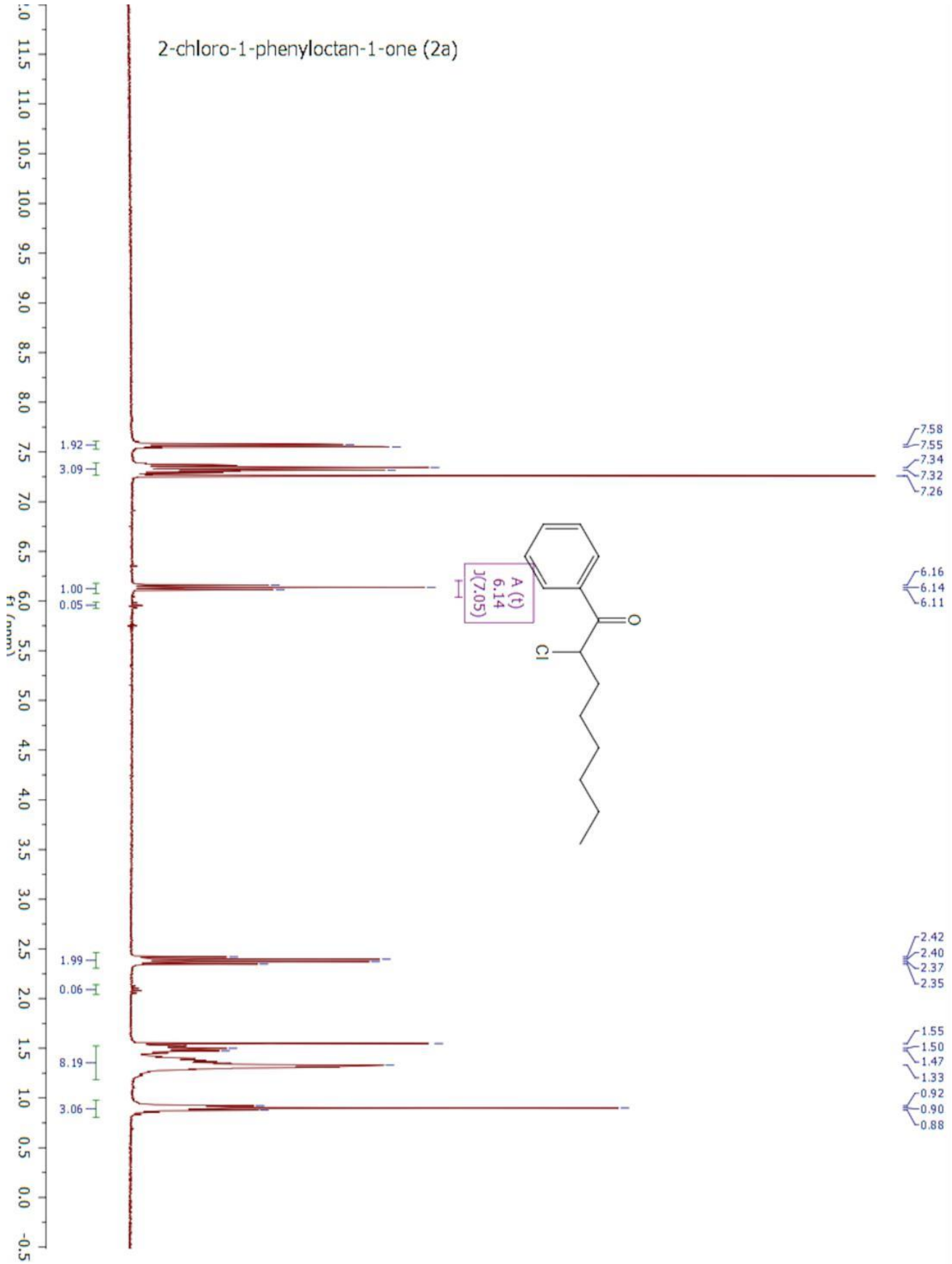

(Z)-1-chloro-1-(4-methoxyphenyl)-1-propene (1m)
159.73
133.56
131.33
127.72
120.76
113.73
77.58
77.36
77.16
76.74
55.49
15.21
O
Cl
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

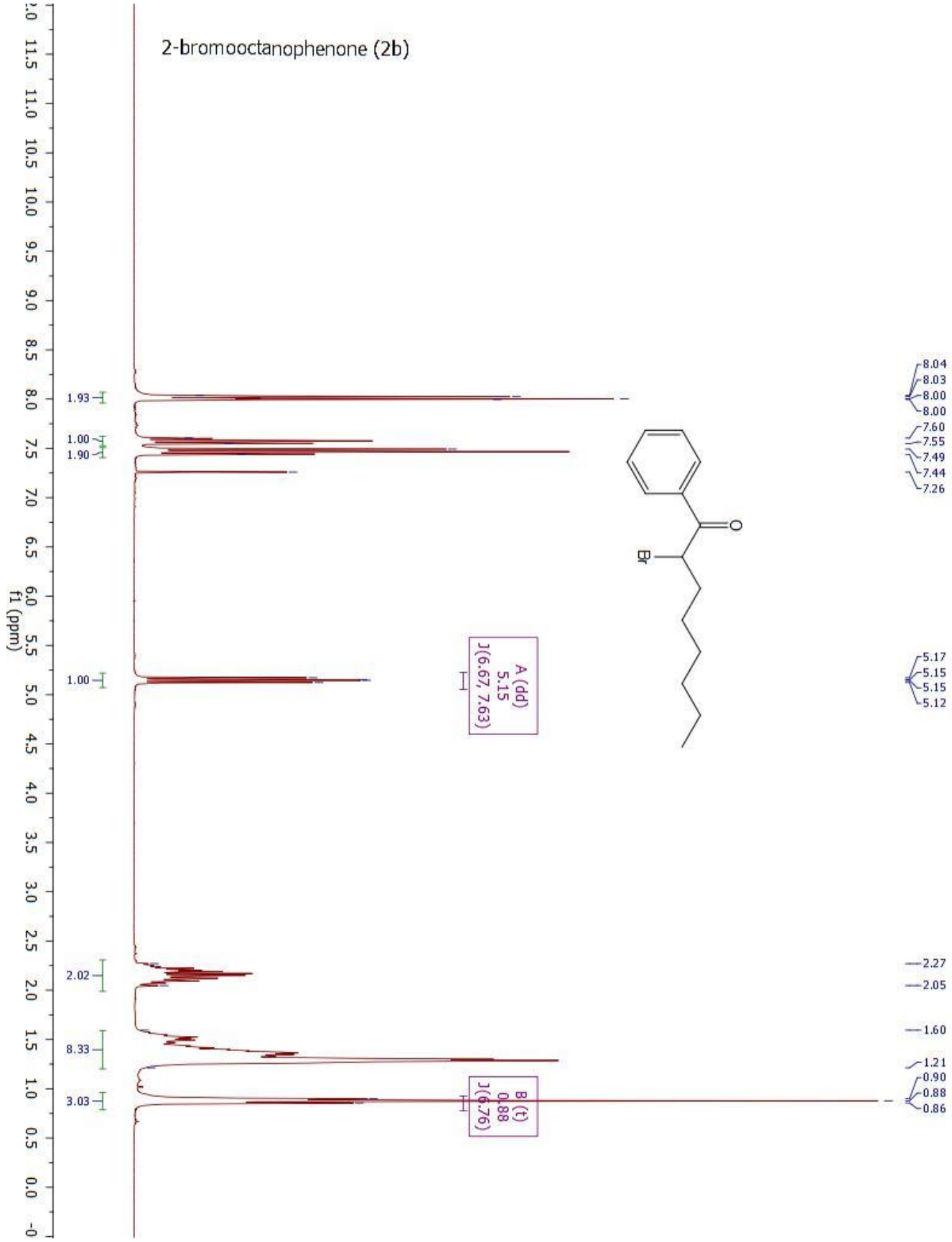

(Z)-1-chloro-1-(3-trifluoromethyl)-1-propene (1n)
A (d) 7.74 J(7.82)
B (d) 7.55 J(7.78)
C (t) 7.46 J(7.77)
D (q) 6.29 J(6.72)
E (d) 1.98 J(6.72)
0.99
1.00
0.99
0.97
1.00
3.02
7.80
7.75
7.72
7.57
7.54
7.49
7.46
7.44
7.26
6.33
6.30
6.28
6.26
1.99
1.97
1.54
F
F
F
Cl
f1 (ppm)

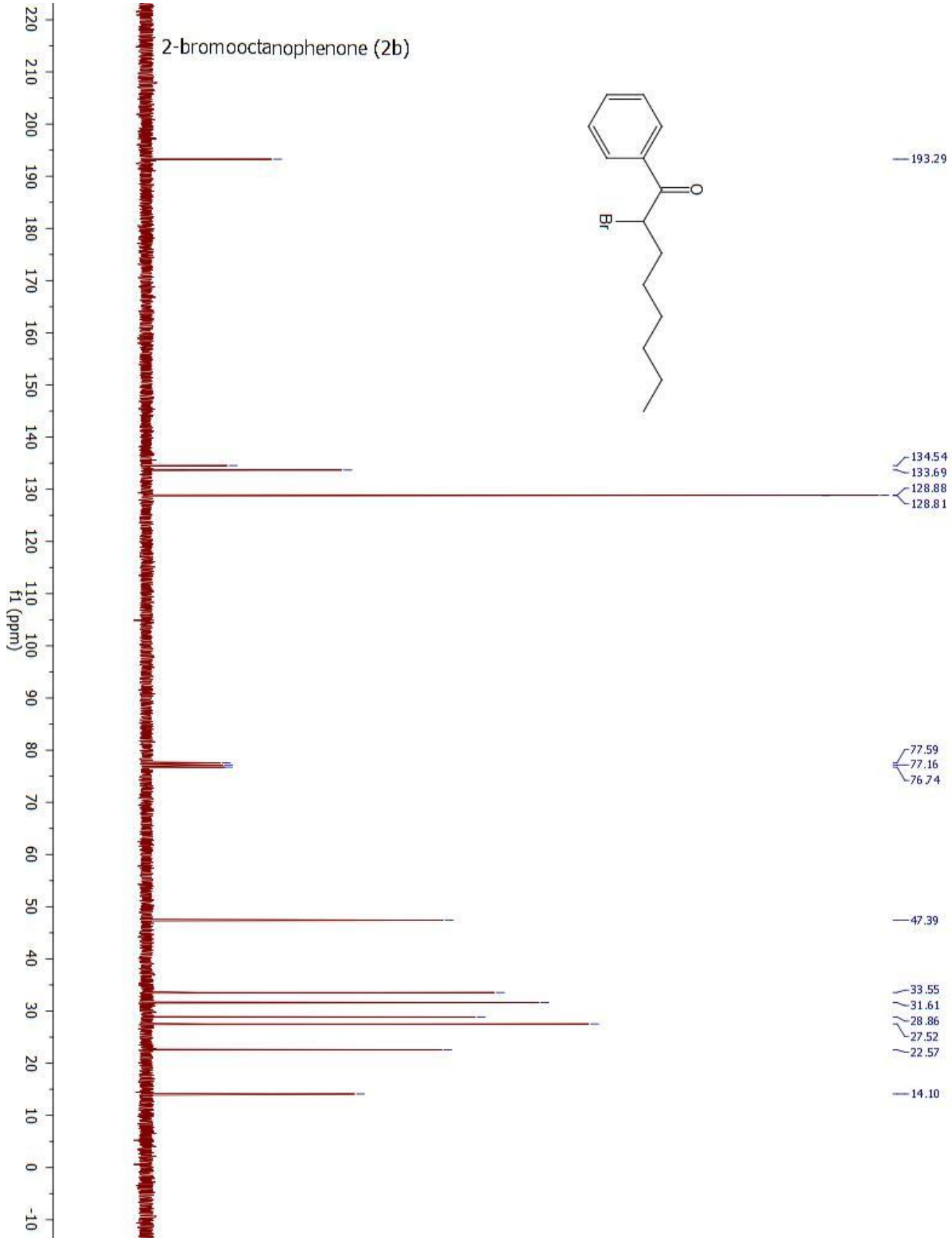

(Z)-1-chloro-1-(3-trifluoromethyl)-1-propene (1n)
f1 (ppm)
139.30
132.51
131.60
131.17
130.74
130.31
129.61
129.59
128.95
125.94
125.02
124.97
124.92
124.87
124.37
123.35
123.30
123.24
123.19
122.33
118.72
77.58
77.16
77.16
76.74
15.34
F
F
F
Cl

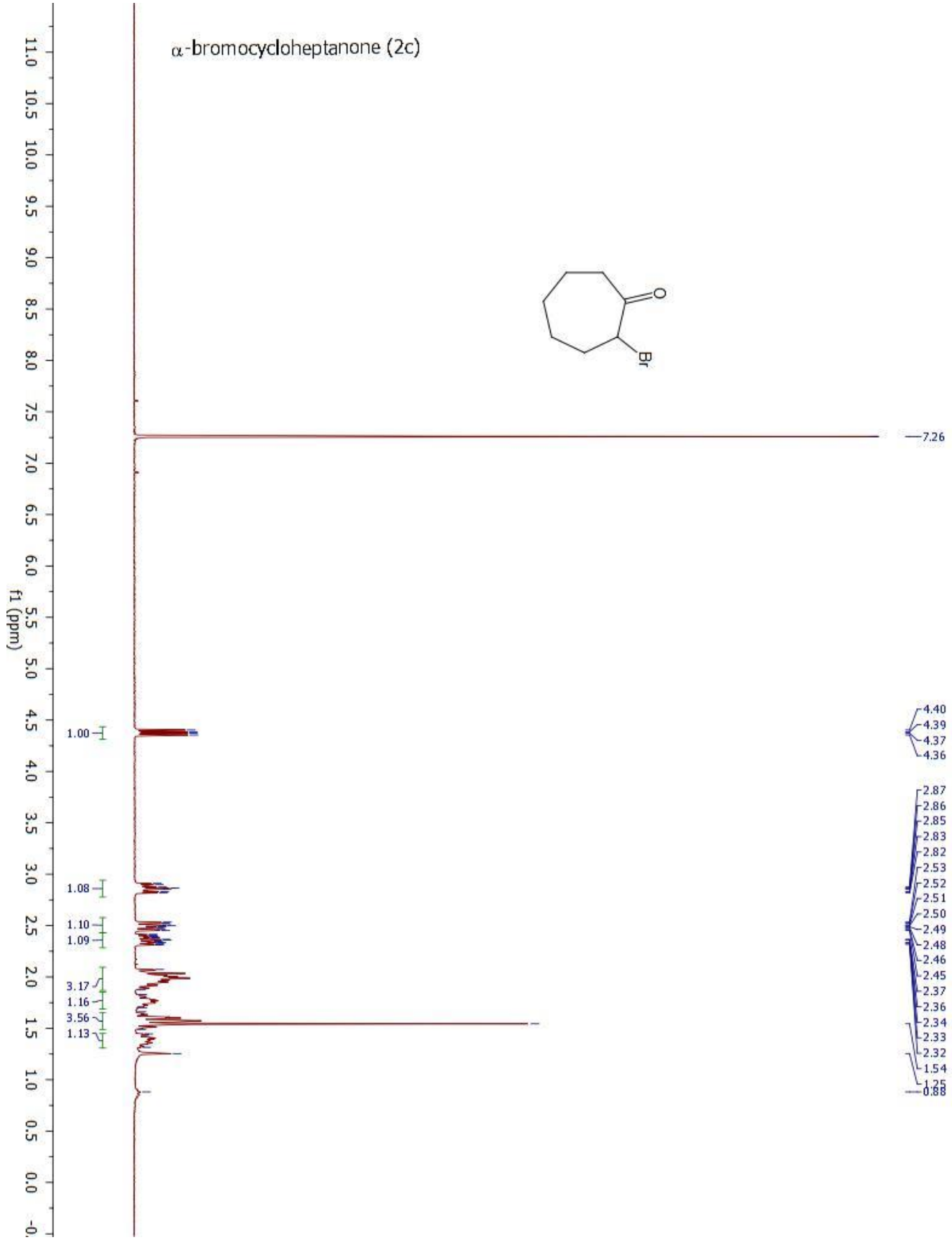

(Z)-(1-chloroethene-1,2-diyl)dibenzene (1o)
4.03
6.23
1.02
7.75
7.71
7.70
7.42
7.40
7.26
7.08
1.54
Cl
f1 (ppm)

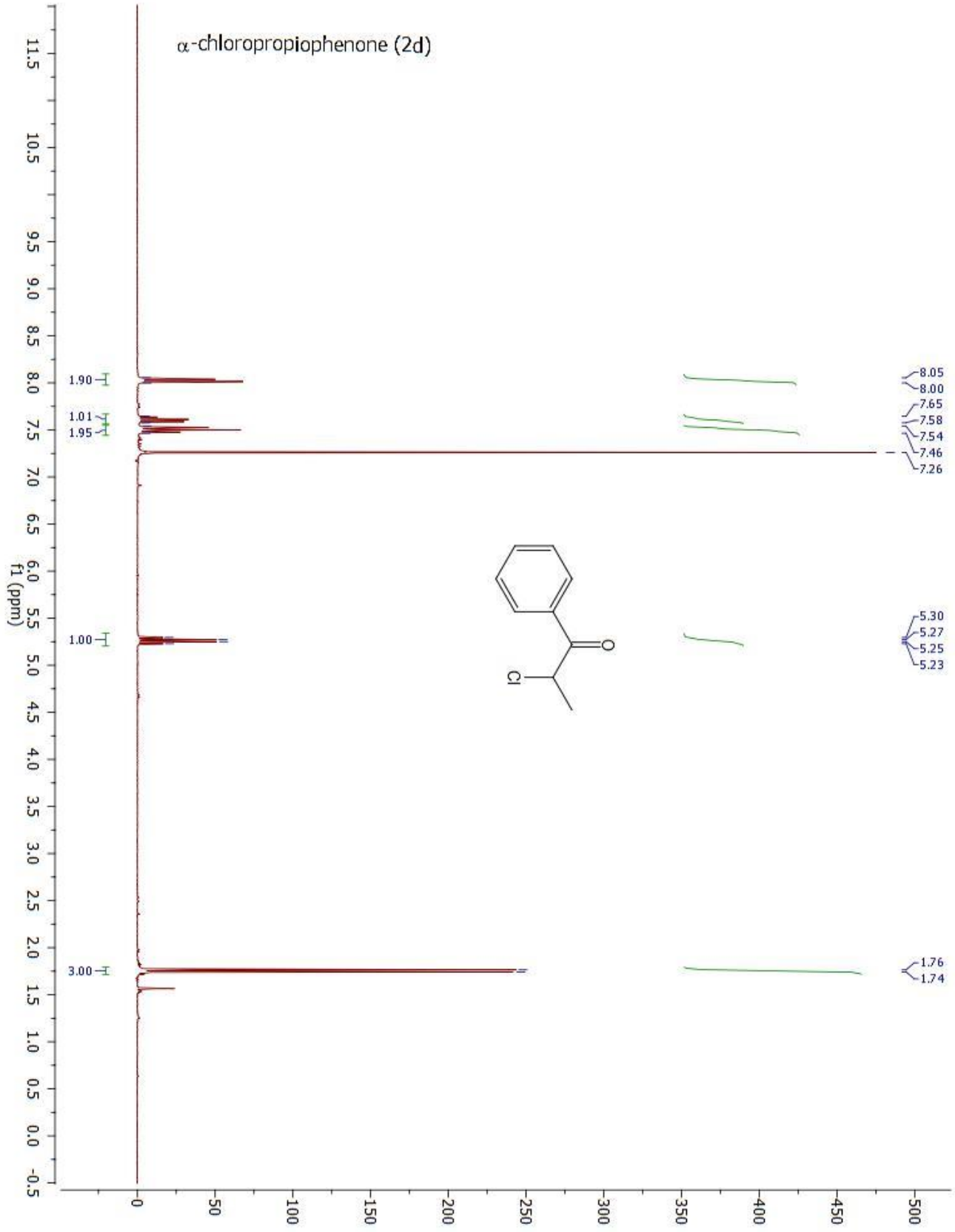

(Z)-(1-chloroethene-1,2-diyl)dibenzene (1o)
129.64
128.93
128.58
128.46
128.18
126.90
126.26
139.41
135.40
132.21
129.60
128.89
128.55
128.43
128.15
126.86
126.23
77.58
77.16
76.74
Cl
f1 (ppm)

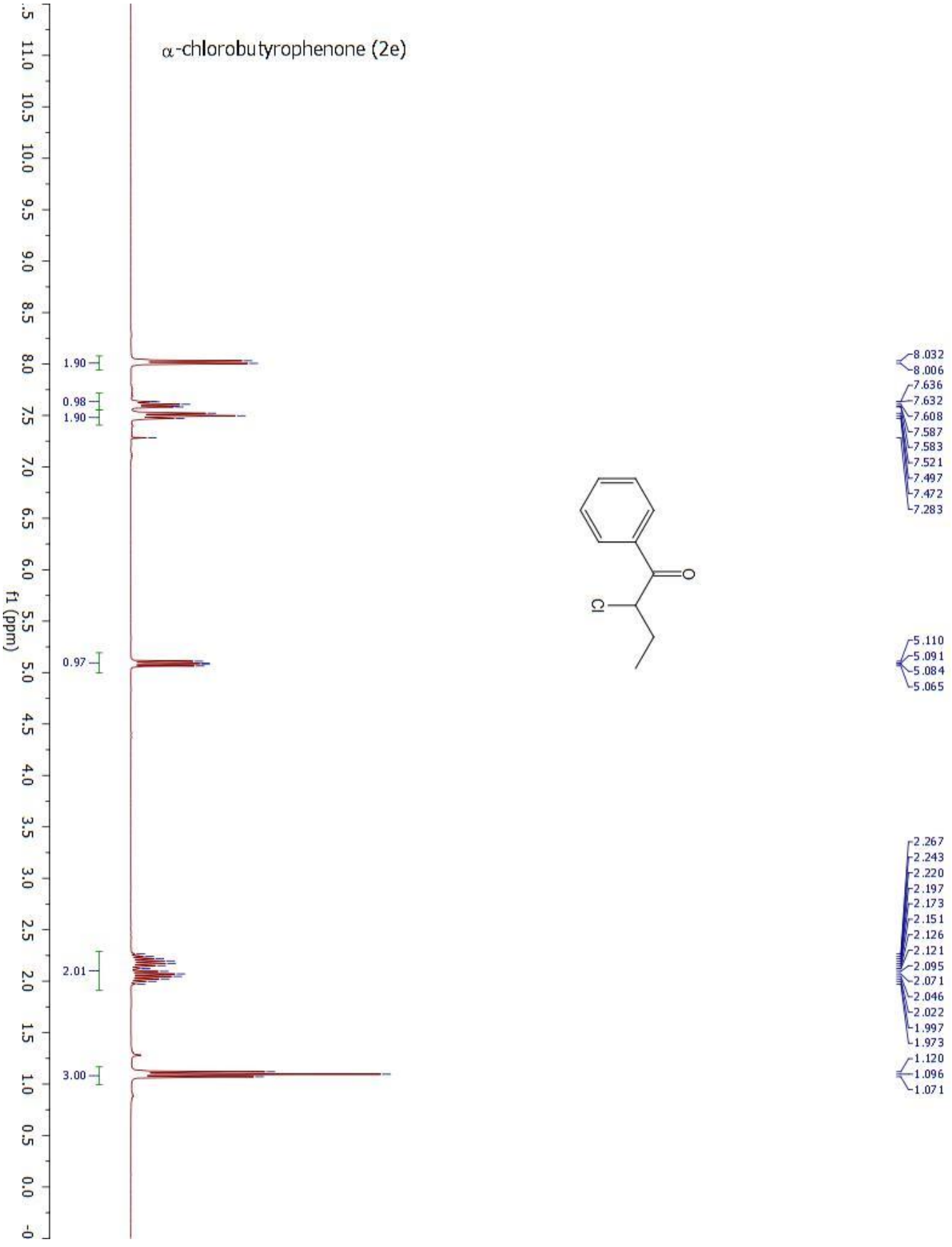

2-chloro-1-phenyloctan-1-one (2a)
1.92
3.09
1.00
0.05
1.99
0.06
8.19
3.06
A (t)
6.14
J(7.05)
O
Cl
7.58
7.55
7.34
7.32
7.26
6.16
6.14
6.11
2.42
2.40
2.37
2.35
1.55
1.50
1.47
1.33
0.92
0.90
0.88
f1 (ppm)

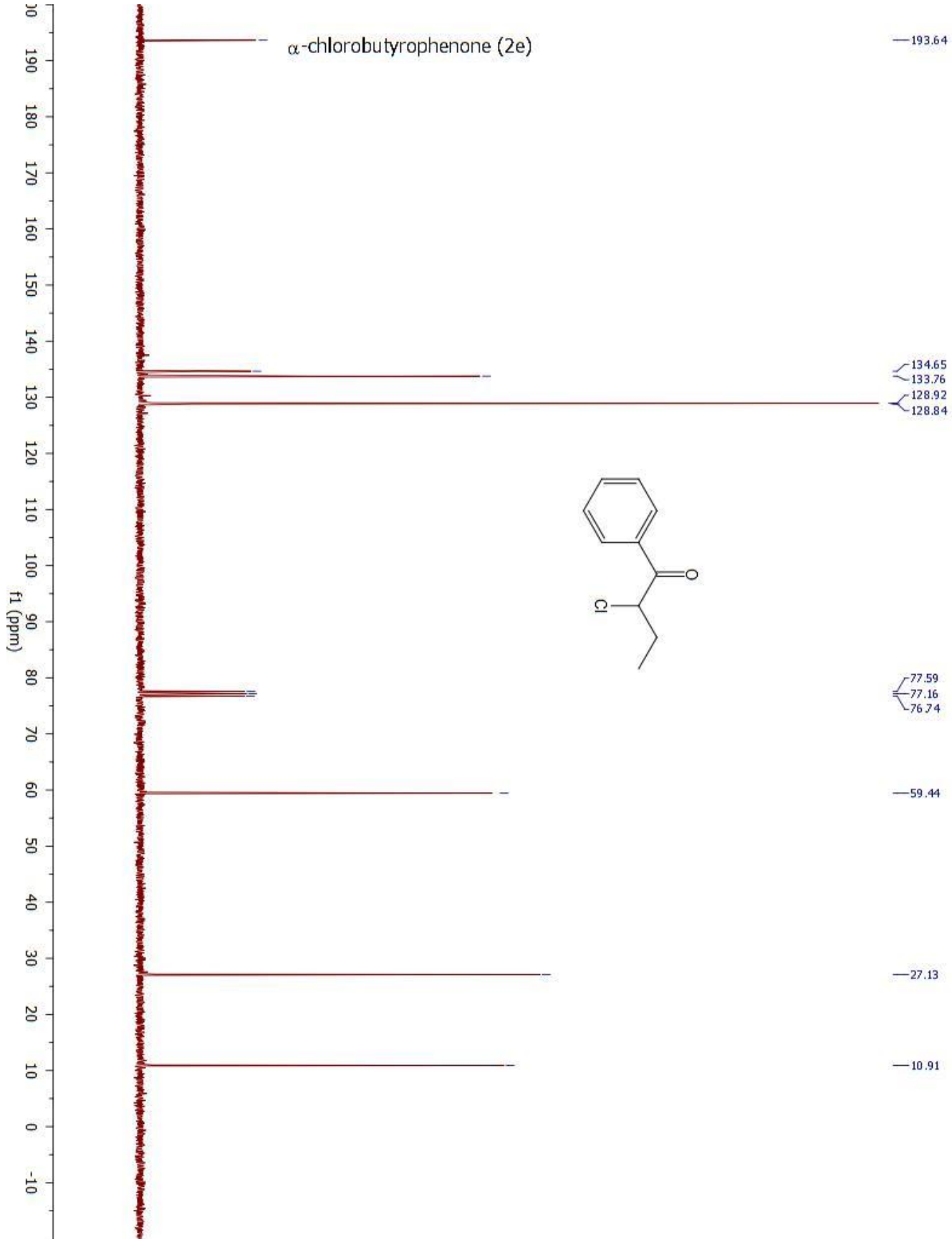

2-bromooctanophenone (2b)
f1 (ppm)
1.93
1.00
1.90
1.00
2.02
8.33
3.03
A (dd)
5.15
J(6.67, 7.63)
B (t)
0.88
J(6.76)
Br
O
8.04
8.03
8.00
8.00
7.60
7.55
7.49
7.44
7.26
5.17
5.15
5.15
5.12
2.27
2.05
1.60
1.21
0.90
0.88
0.86

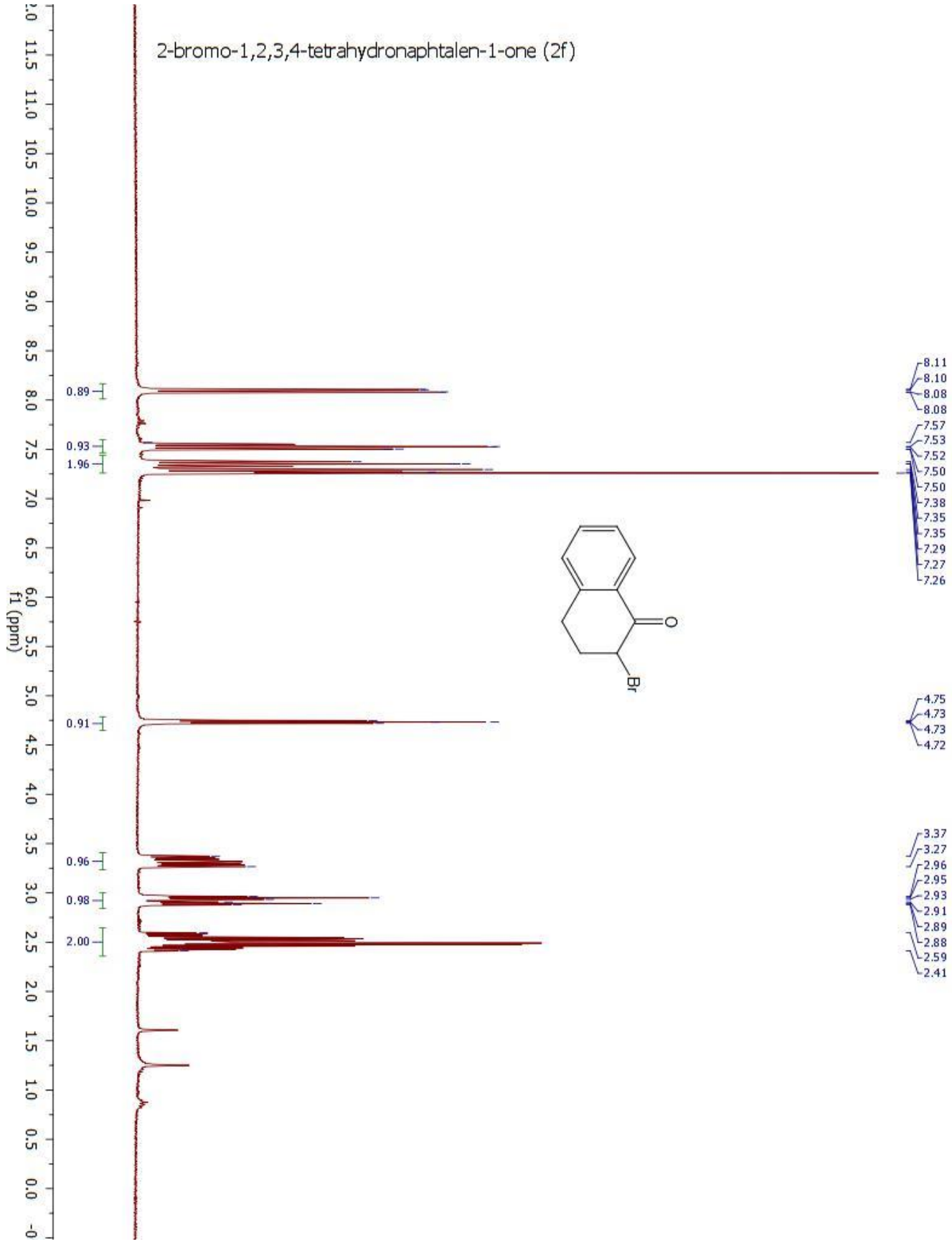

2-bromooctanophenone (2b)
O
Br
193.29
134.54
133.69
128.88
128.81
77.59
77.16
76.74
47.39
33.55
31.61
28.86
27.52
22.57
14.10
f1 (ppm)

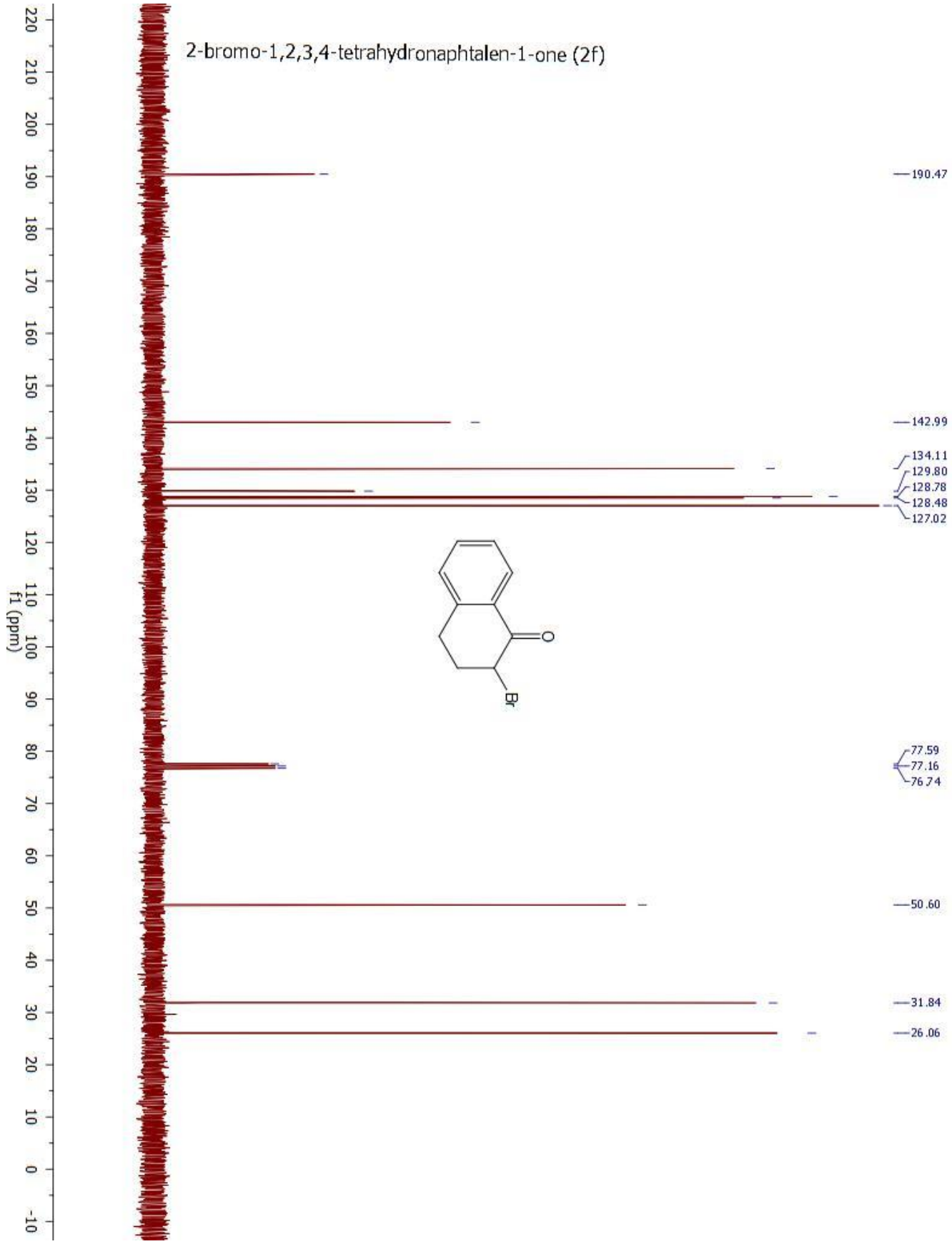

α-bromocycloheptanone (2c)
O
Br
f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
7.26
4.40
4.39
4.37
4.36
2.87
2.86
2.85
2.83
2.82
2.53
2.52
2.51
2.50
2.49
2.48
2.46
2.45
2.37
2.36
2.34
2.33
2.32
1.54
1.25
0.88
1.00
1.08
1.10
1.09
3.17
1.16
3.56
1.13

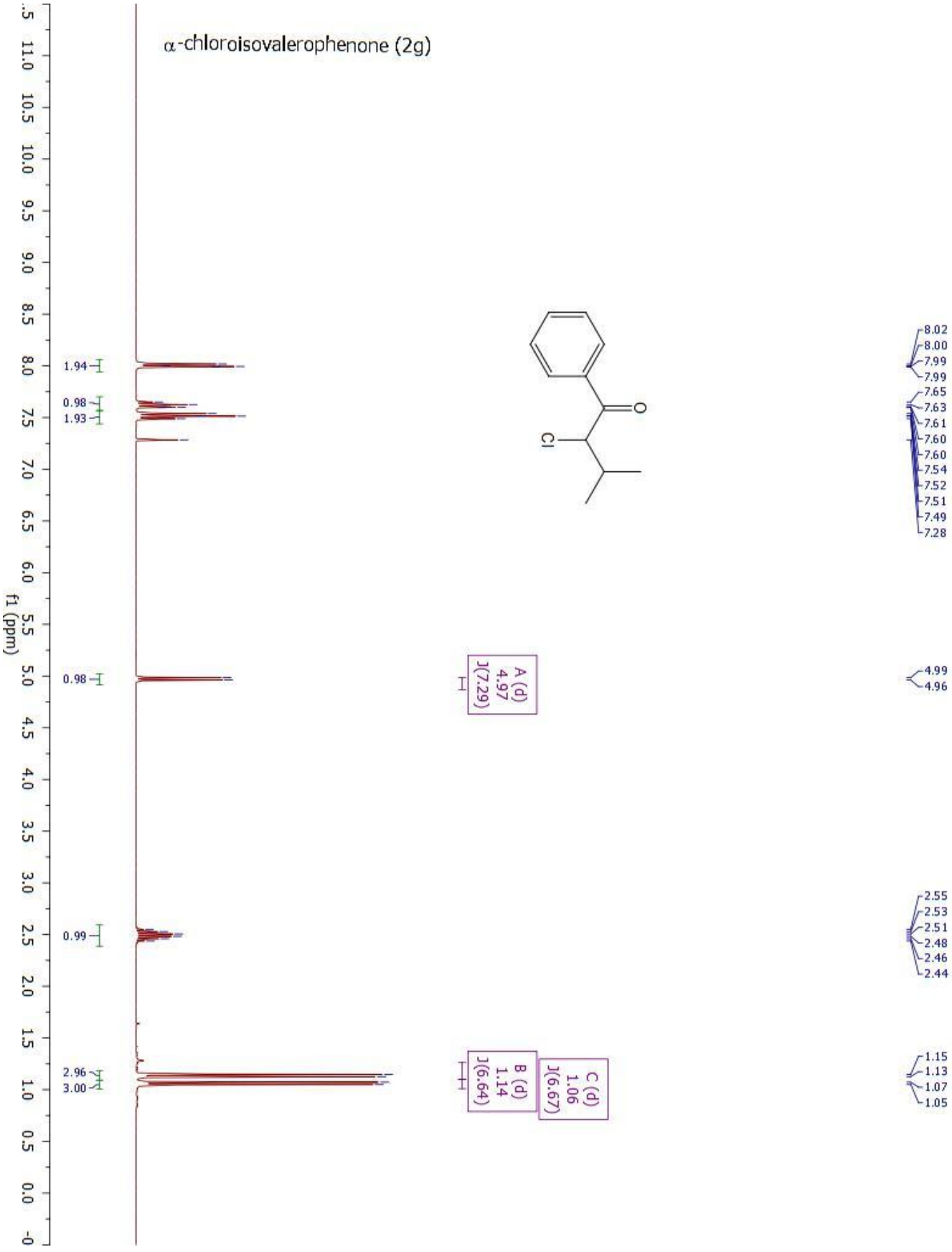

α-chloropropiophenone (2d)
1.90
1.01
1.95
1.00
3.00
8.05
8.00
7.65
7.58
7.54
7.46
7.26
5.30
5.27
5.25
5.23
1.76
1.74
O
Cl
f1 (ppm)

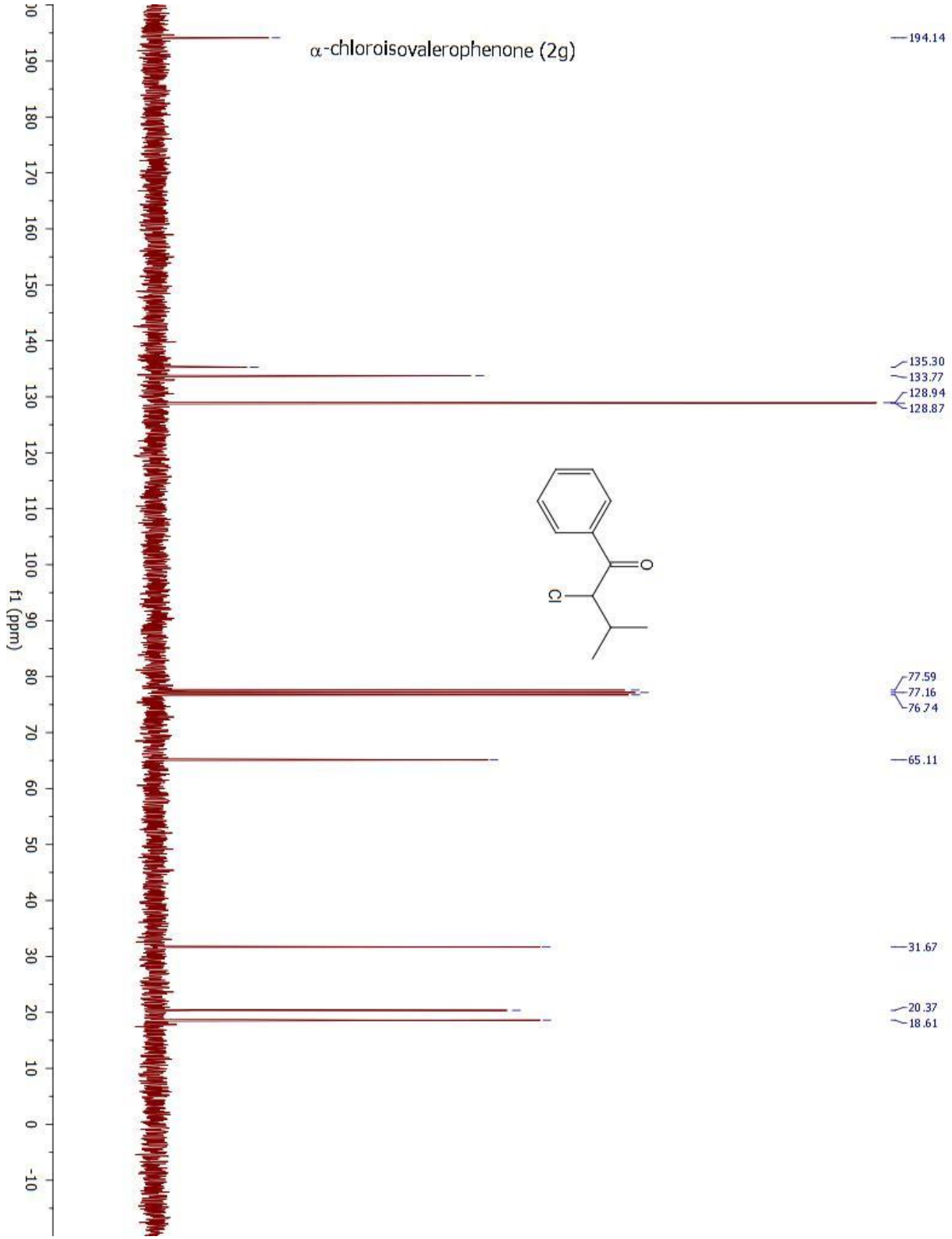

α-chlorobutyrophenone (2e)
f1 (ppm)
1.90
0.98
1.90
0.97
2.01
3.00
Cl
O
8.032
8.006
7.636
7.632
7.608
7.587
7.583
7.521
7.497
7.472
7.283
5.110
5.091
5.084
5.065
2.267
2.243
2.220
2.197
2.173
2.151
2.126
2.121
2.095
2.071
2.046
2.022
1.997
1.973
1.120
1.096
1.071

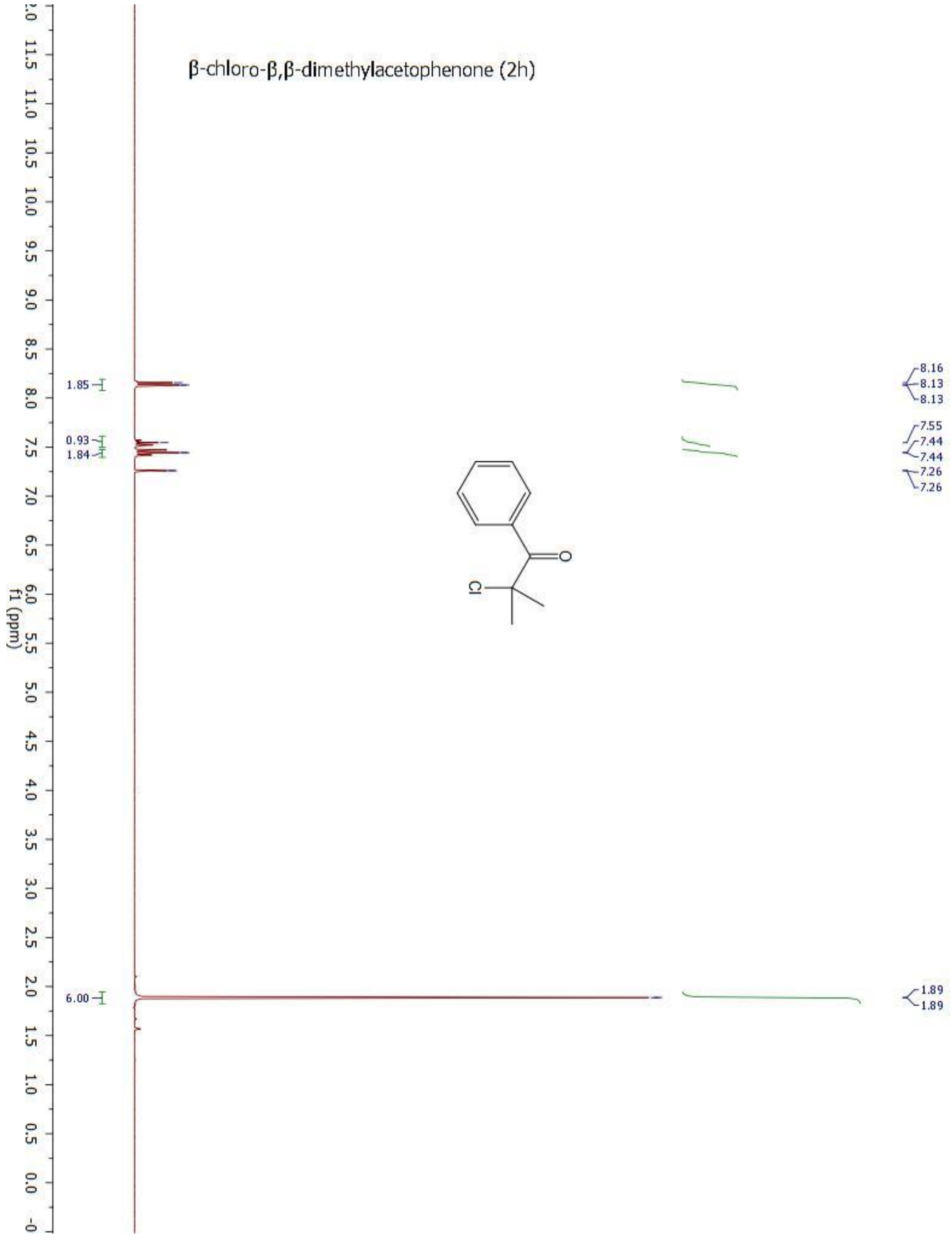

α-chlorobutyrophenone (2e)
193.64
134.65
133.76
128.92
128.84
77.59
77.16
76.74
59.44
27.13
10.91
O
Cl
f1 (ppm)


2-bromo-1,2,3,4-tetrahydronaphtalen-1-one (2f)
f1 (ppm)
0.89
0.93
1.96
0.91
0.96
0.98
2.00
8.11
8.10
8.08
8.08
7.57
7.53
7.52
7.50
7.50
7.38
7.35
7.35
7.29
7.27
7.26
4.75
4.73
4.73
4.72
3.37
3.27
2.96
2.95
2.93
2.91
2.89
2.88
2.59
2.41
O
Br

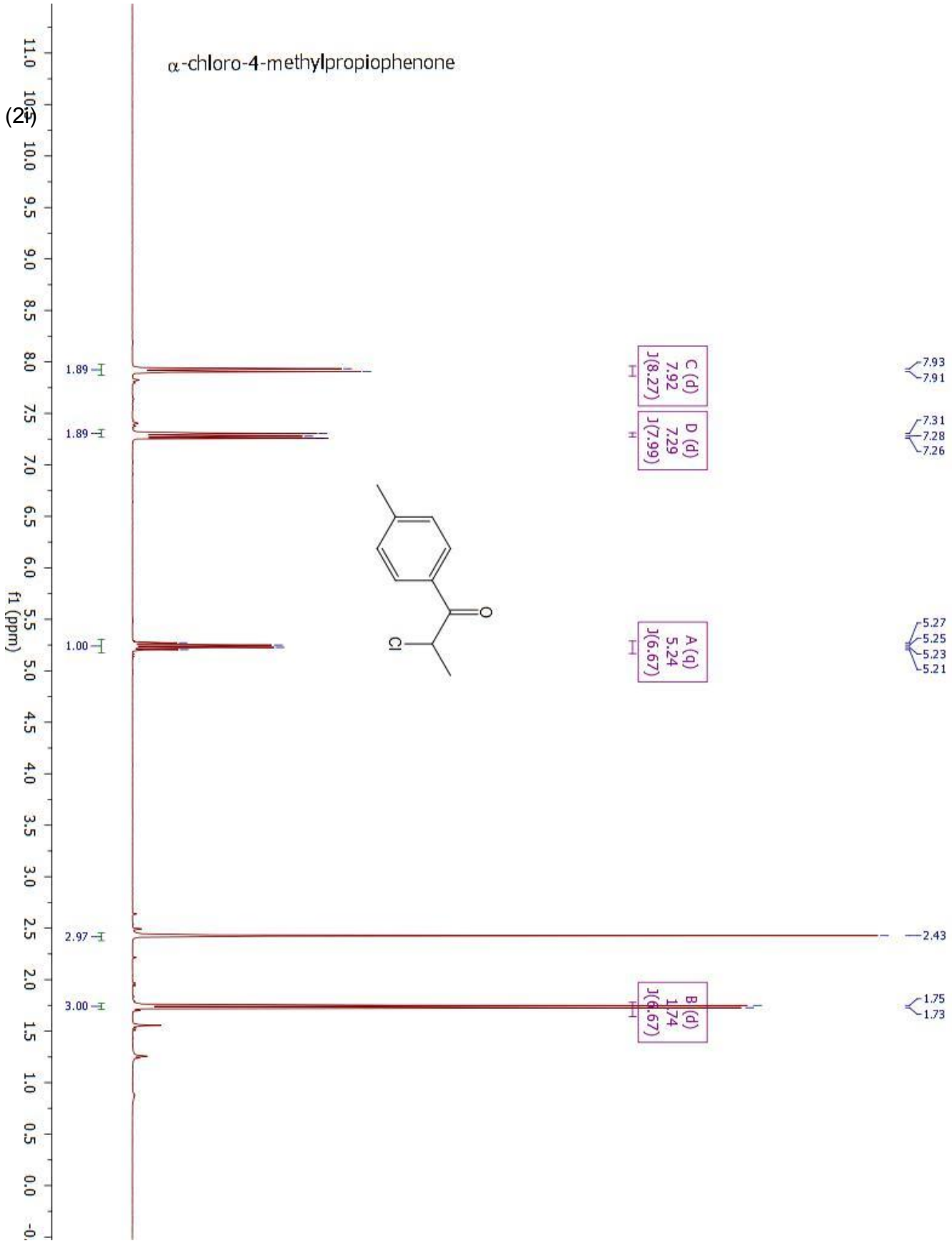

2-bromo-1,2,3,4-tetrahydronaphtalen-1-one (2f)
190.47
142.99
134.11
129.80
128.78
128.48
127.02
77.59
77.16
76.74
50.60
31.84
26.06
O
Br
f1 (ppm)


α-chloroisovalerophenone (2g)
f1 (ppm)
1.94
0.98
1.93
0.98
0.99
2.96
3.00
A (d)
4.97
J(7.29)
B (d)
1.14
J(6.64)
C (d)
1.06
J(6.67)
Cl
O
8.02
8.00
7.99
7.99
7.65
7.63
7.61
7.60
7.60
7.54
7.52
7.51
7.49
7.28
4.99
4.96
2.55
2.53
2.51
2.48
2.46
2.44
1.15
1.13
1.07
1.05

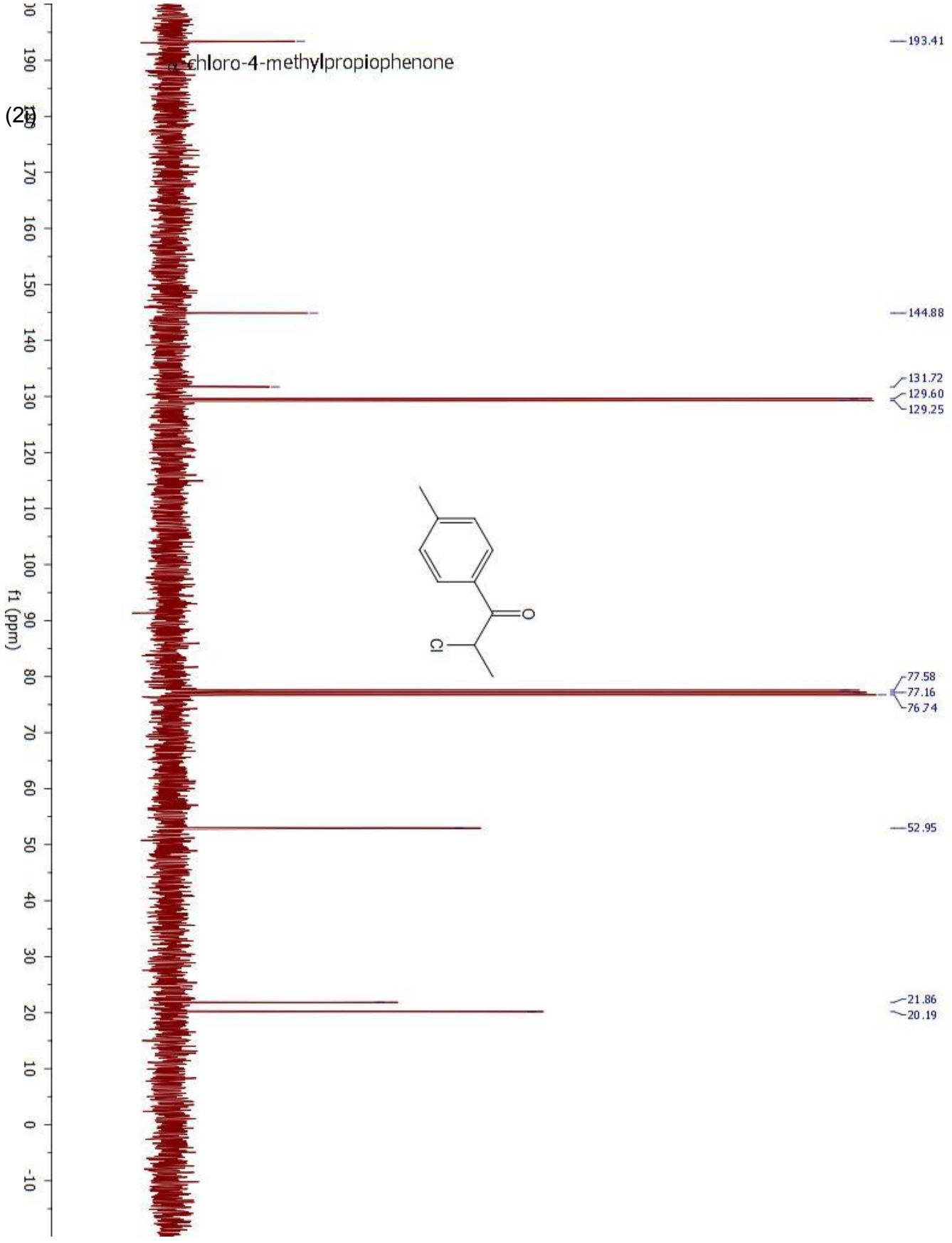

α-chloroisovalerophenone (2g)
194.14
135.30
133.77
128.94
128.87
77.59
77.16
76.74
65.11
31.67
20.37
18.61
O
Cl
f1 (ppm)

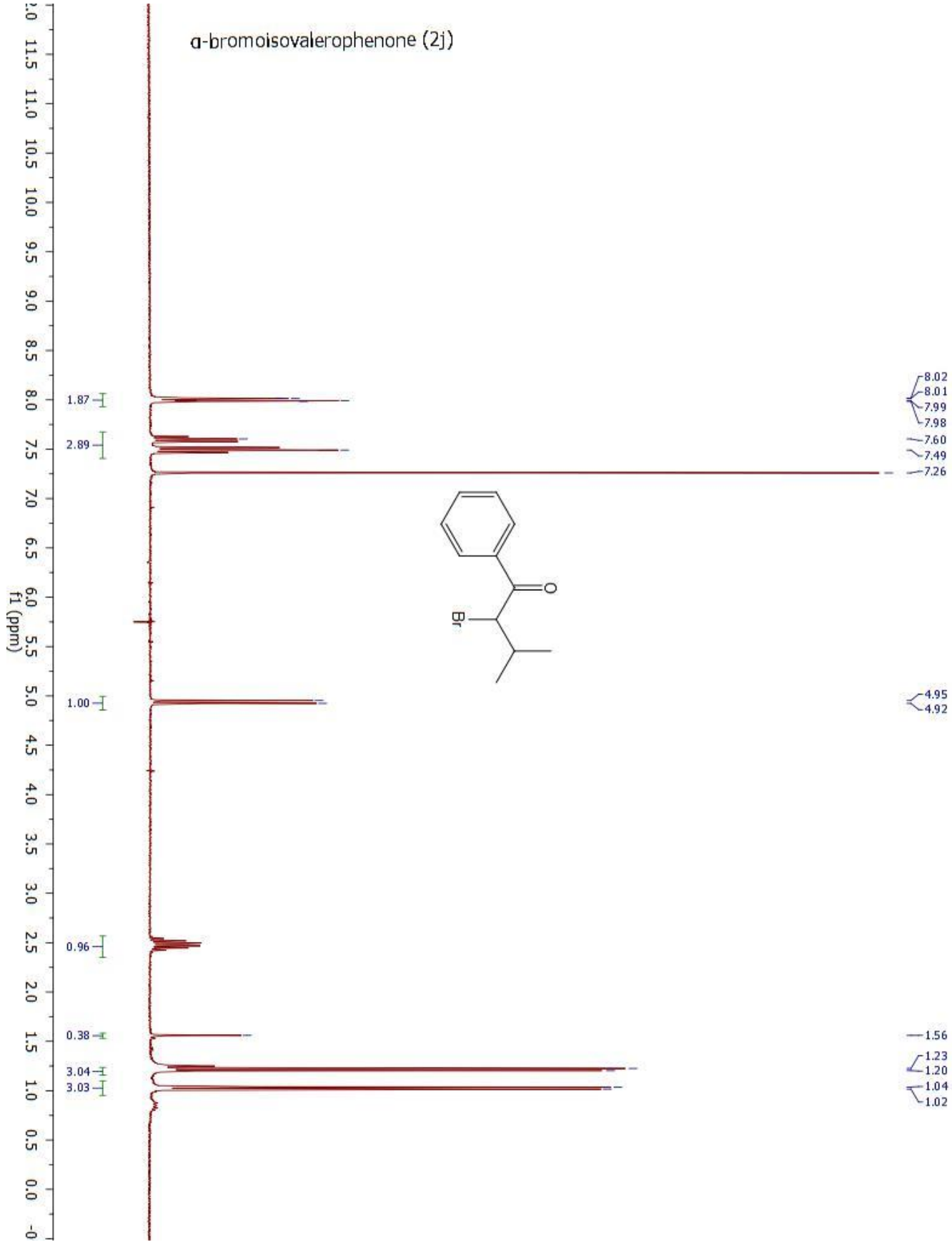

β-chloro-β,β-dimethylacetophenone (2h)
1.85
0.93
1.84
6.00
8.16
8.13
8.13
7.55
7.44
7.44
7.26
7.26
1.89
1.89
O
Cl
f1 (ppm)

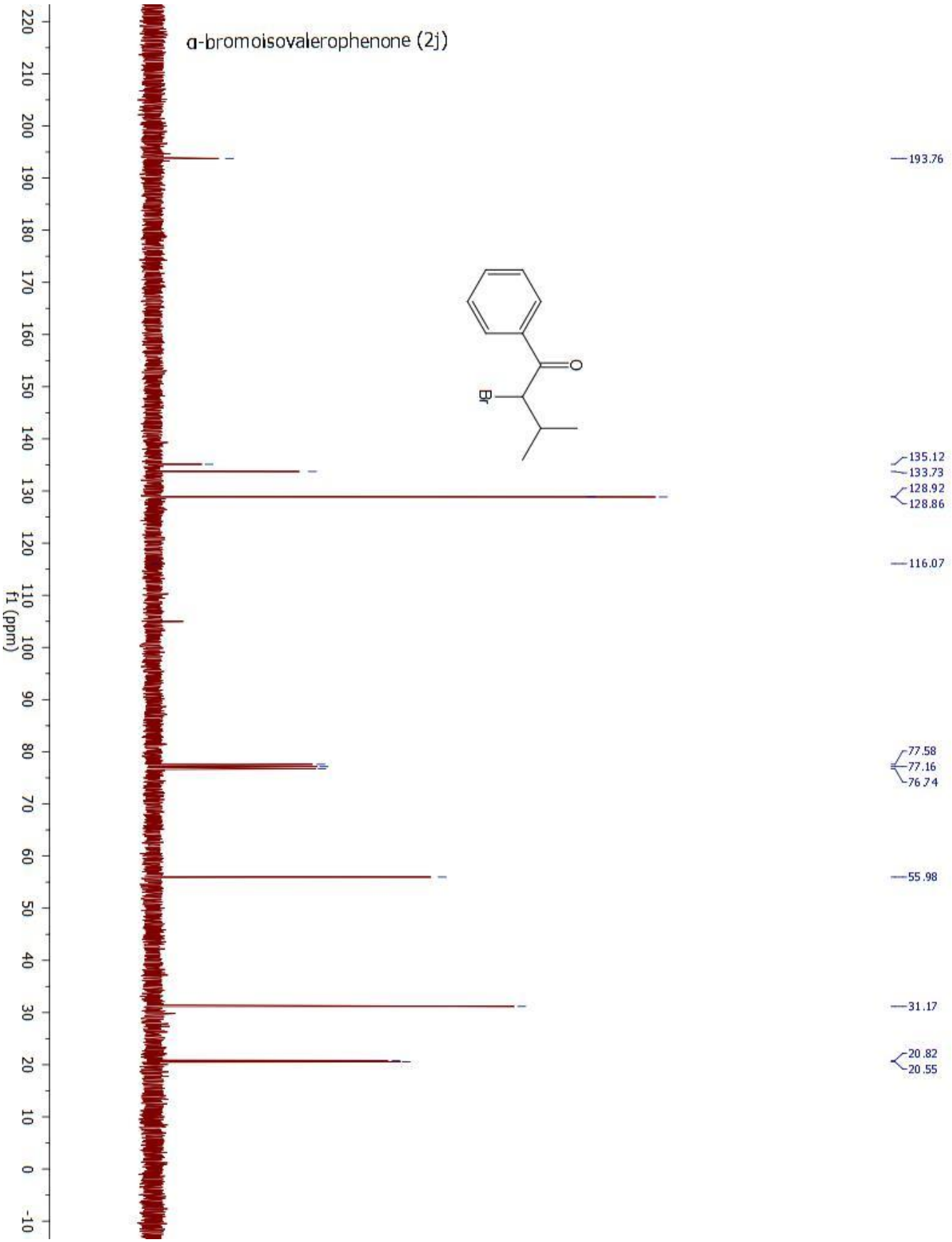
(2f)

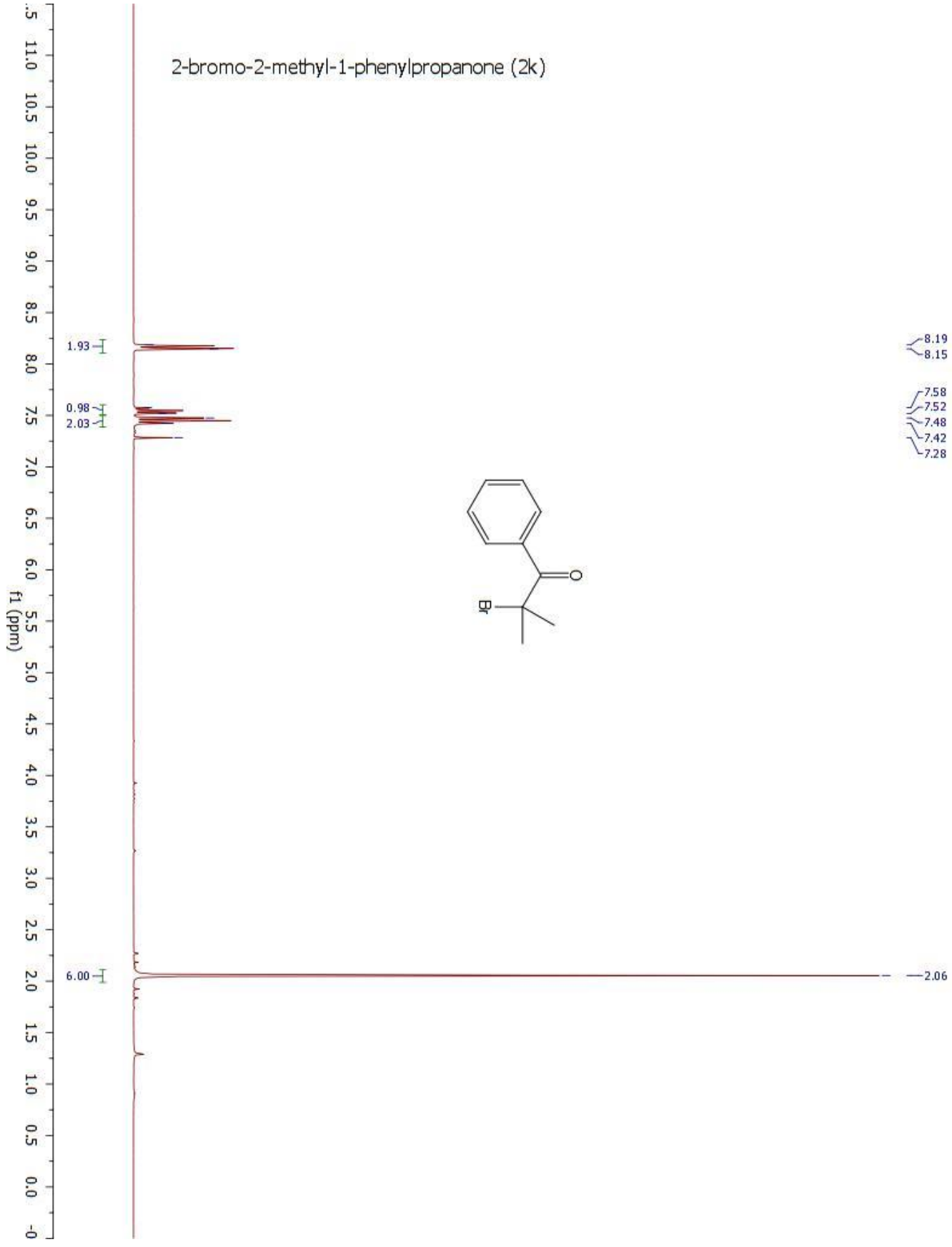

α-chloro-4-methylpropiophenone
f1 (ppm)
1.89
1.89
1.00
2.97
3.00
C (d) 7.92 J(8.27)
D (d) 7.29 J(7.99)
A (q) 5.24 J(6.67)
B (d) 1.74 J(6.67)
7.93
7.91
7.31
7.28
7.26
5.27
5.25
5.23
5.21
2.43
1.75
1.73
O
Cl

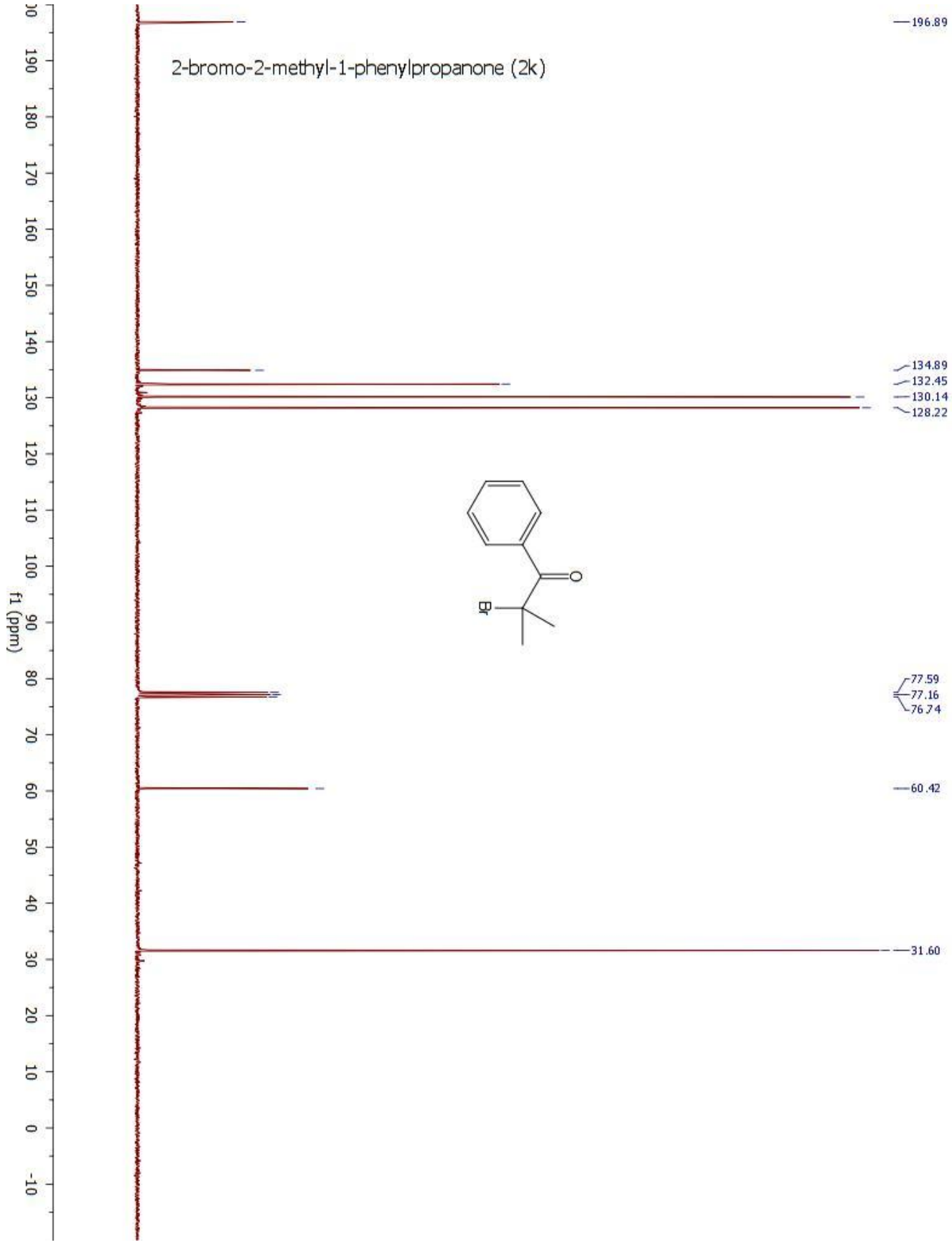
(2g)

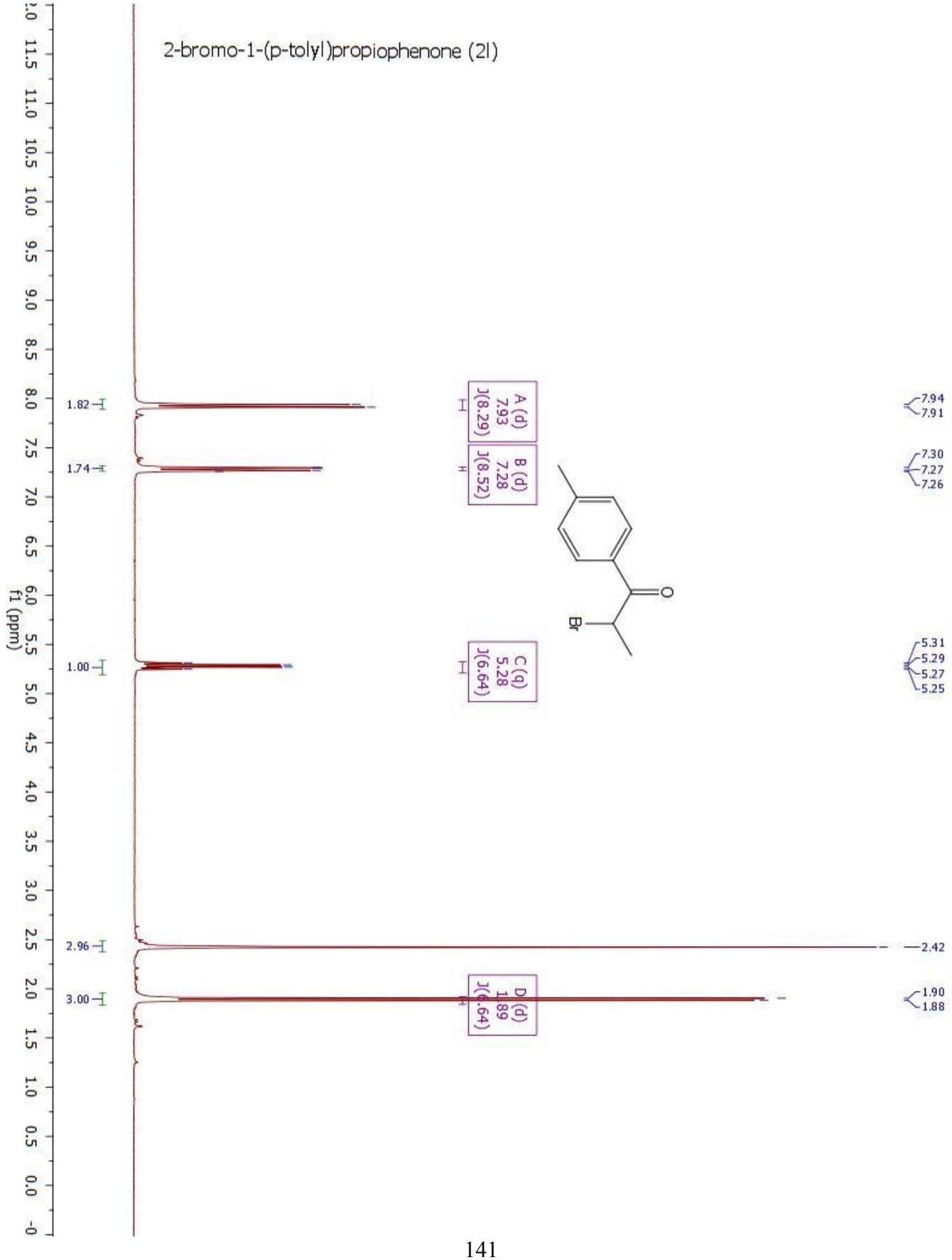

2-chloro-4-methylpropiophenone
193.41
144.88
131.72
129.60
129.25
77.58
77.16
76.74
52.95
21.86
20.19
O
Cl
f1 (ppm)

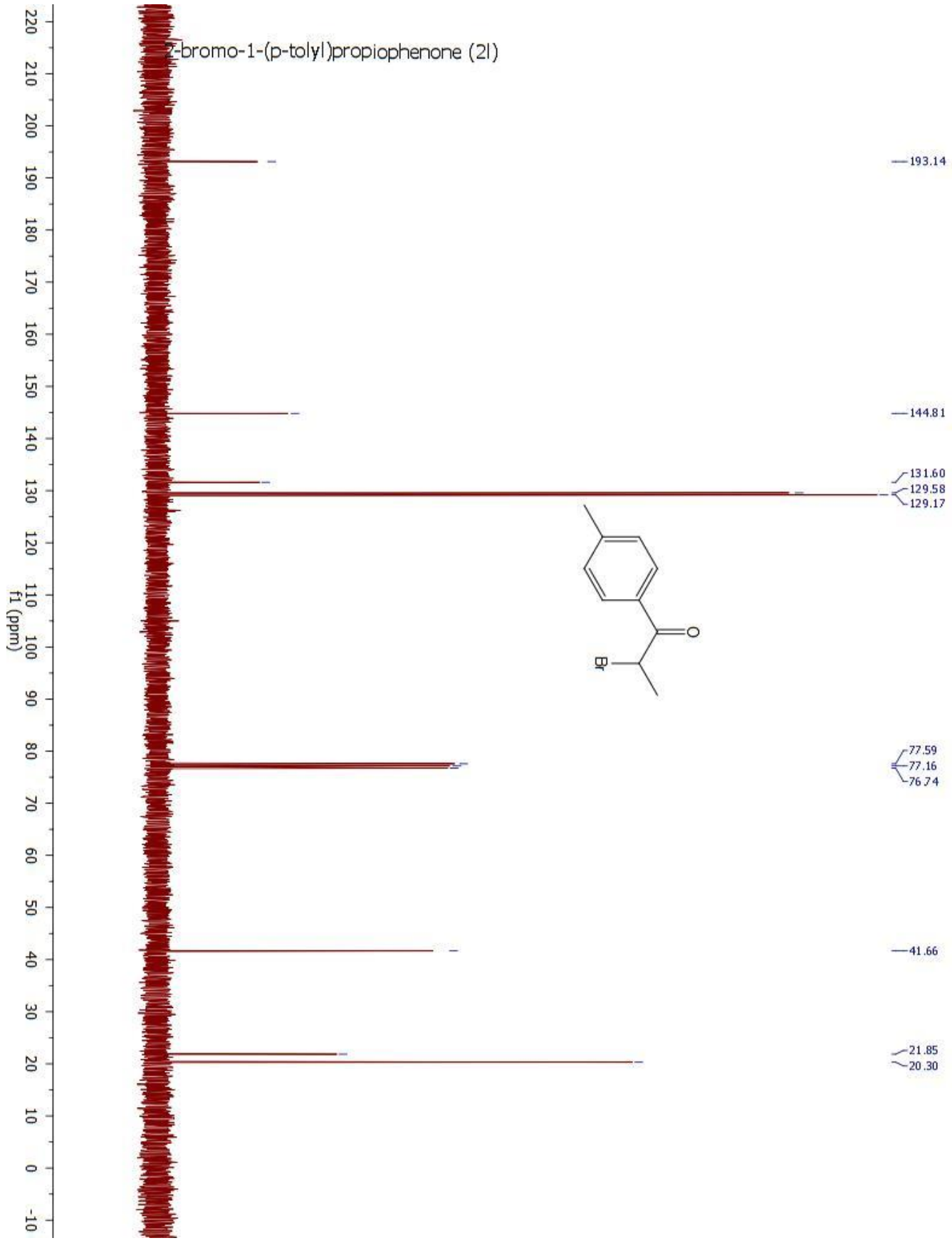

α-bromoisovalerophenone (2j)
f1 (ppm)
1.87
2.89
1.00
0.96
0.38
3.04
3.03
8.02
8.01
7.99
7.98
7.60
7.49
7.26
4.95
4.92
1.56
1.23
1.20
1.04
1.02
O
Br

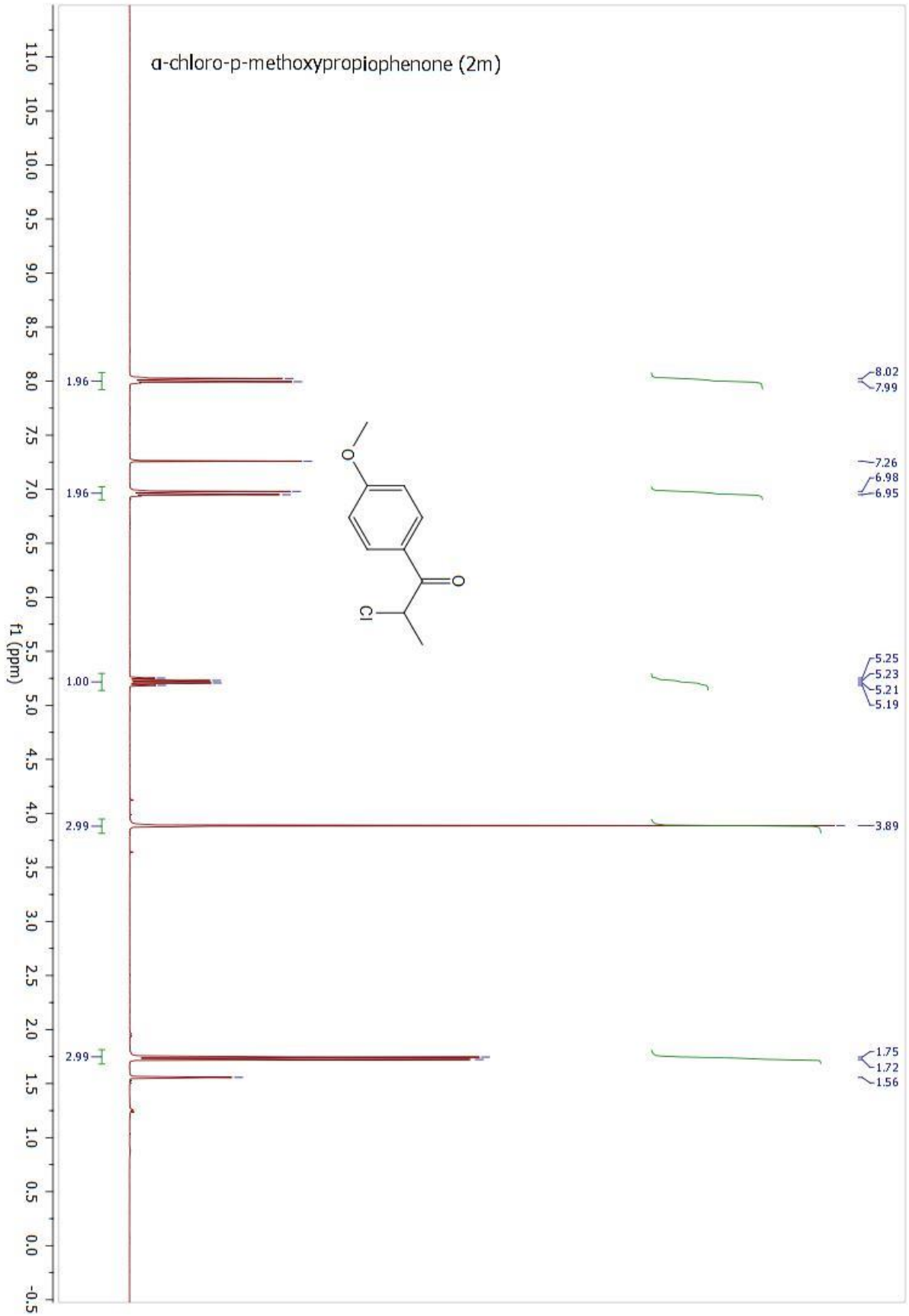

α-bromoisovalerophenone (2j)
193.76
135.12
133.73
128.92
128.86
116.07
77.58
77.16
76.74
55.98
31.17
20.82
20.55
O
Br
f1 (ppm)

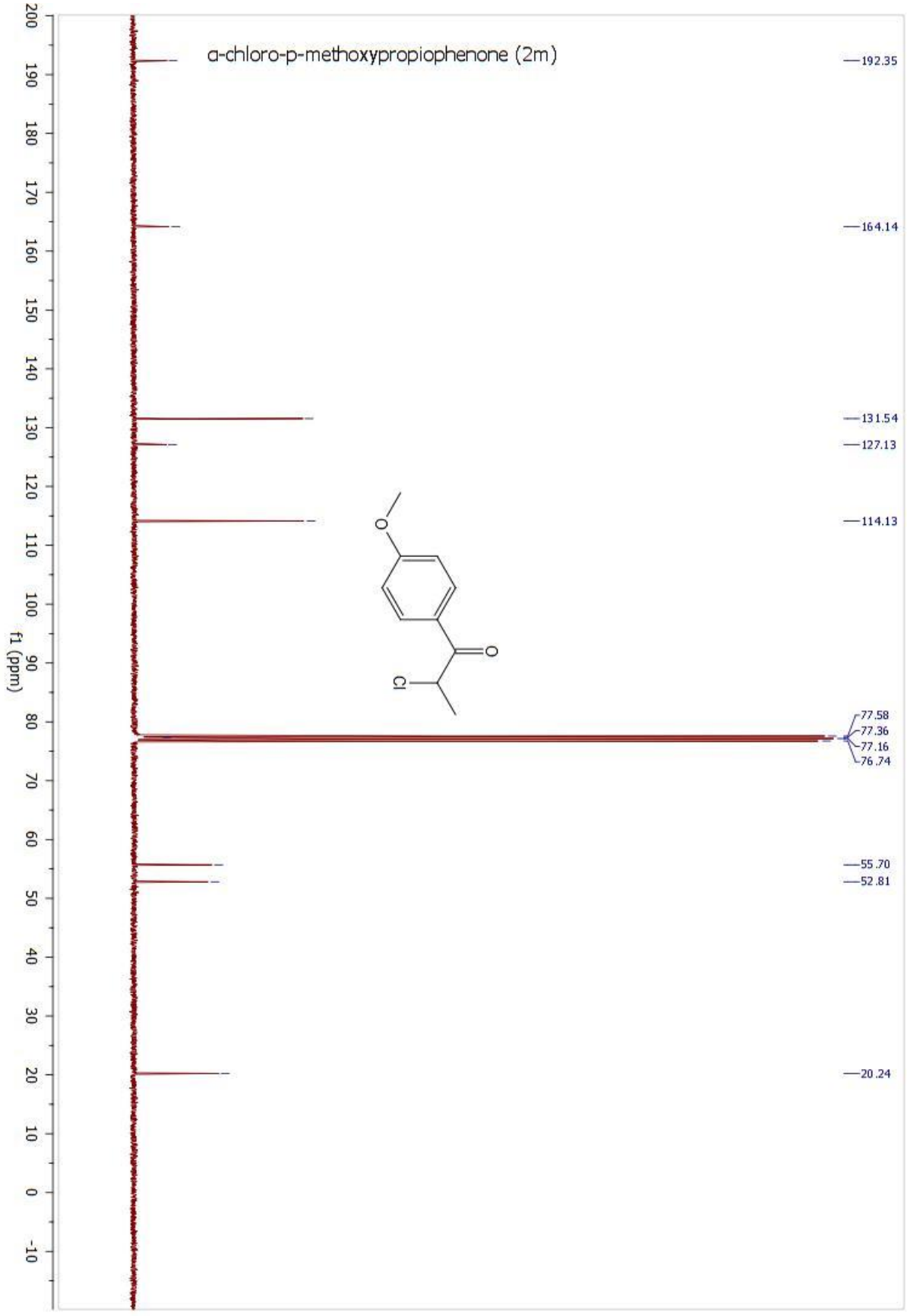

2-bromo-2-methyl-1-phenylpropanone (2k)
1.93
0.98
2.03
6.00
8.19
8.15
7.58
7.52
7.48
7.42
7.28
2.06
O
Br
f1 (ppm)

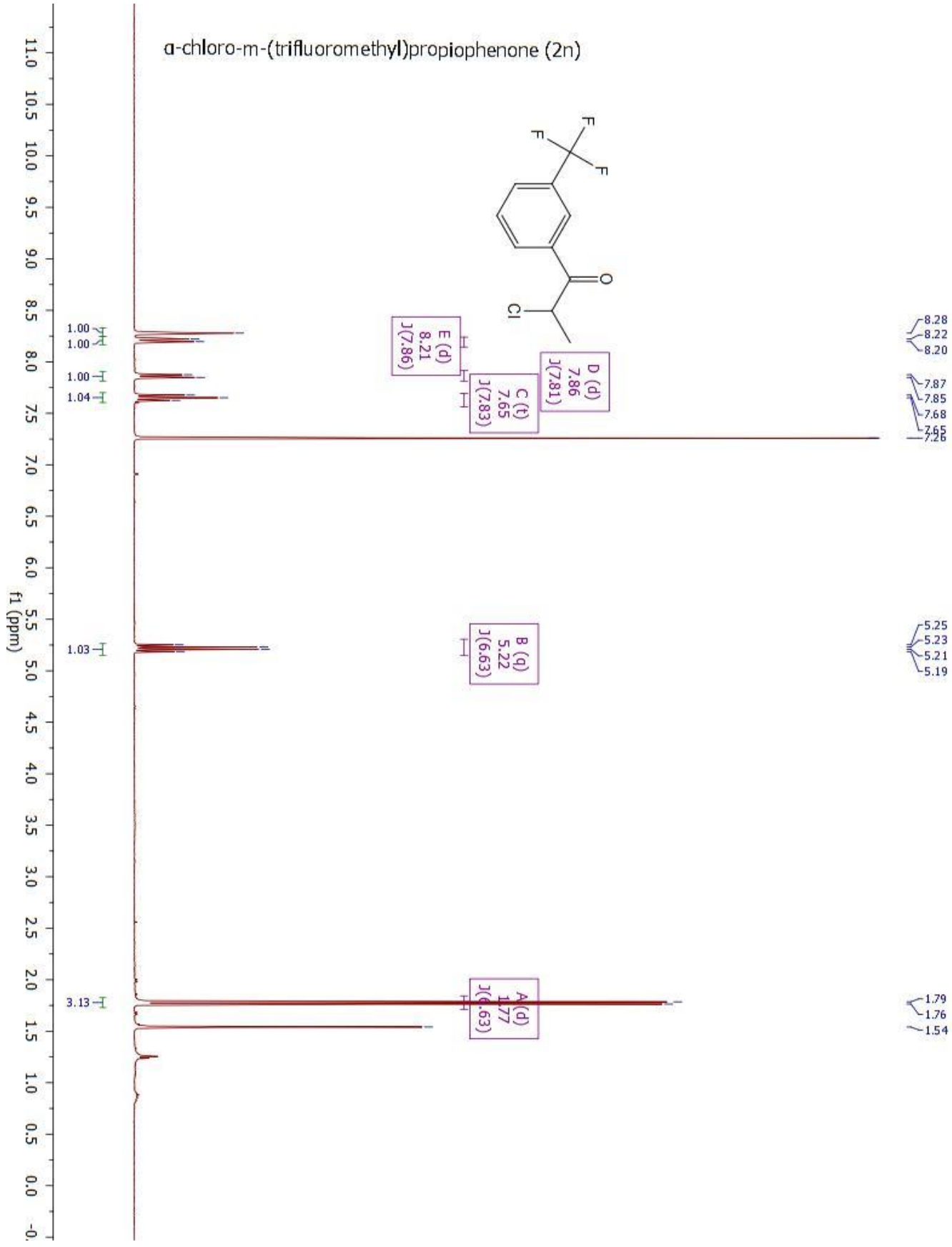

2-bromo-2-methyl-1-phenylpropanone (2k)
196.89
134.89
132.45
130.14
128.22
77.59
77.16
76.74
60.42
31.60
O
Br
f1 (ppm)

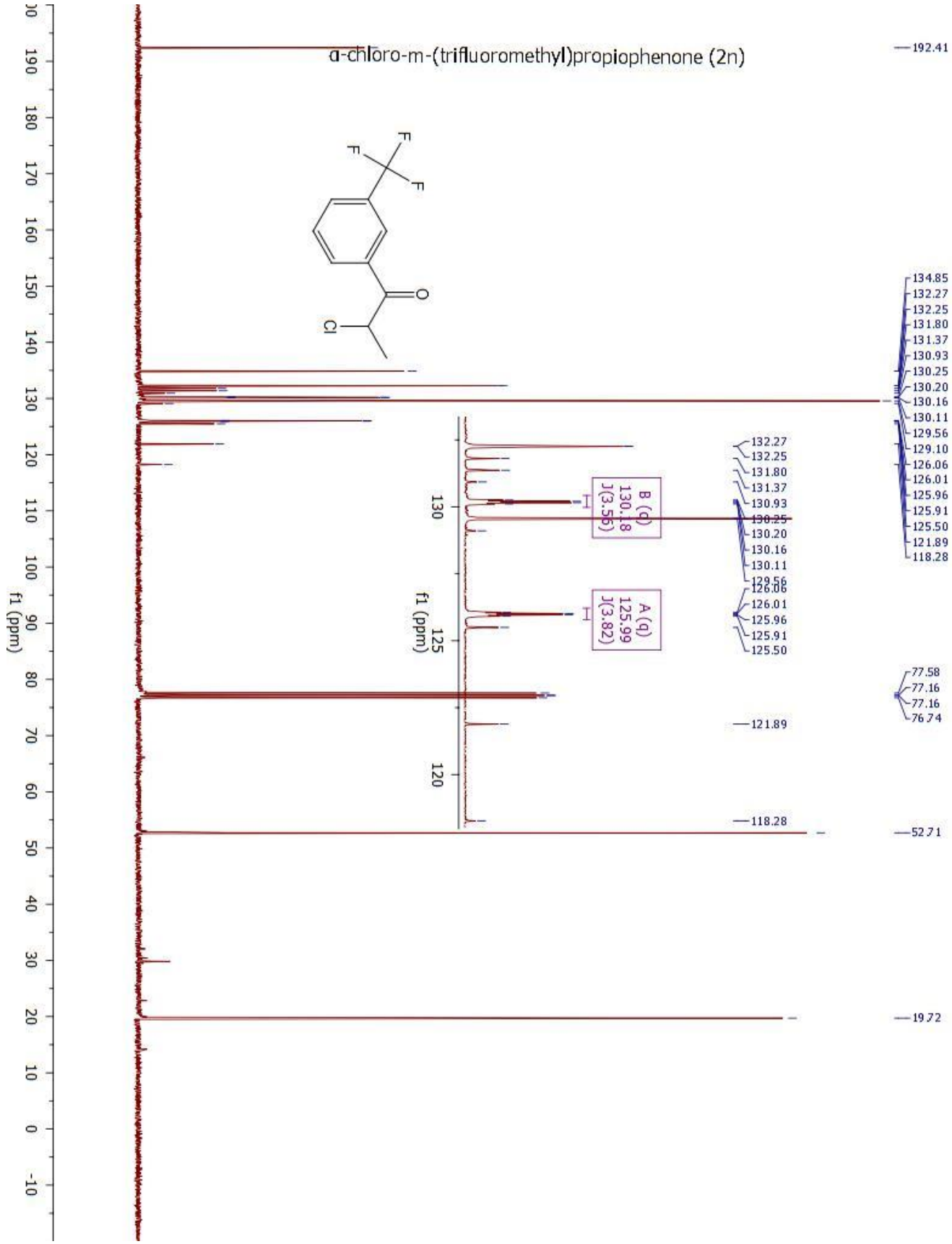

2-bromo-1-(p-tolyl)propiophenone (2l)
f1 (ppm)
1.82
1.74
1.00
2.96
3.00
A (d) 7.93 J(8.29)
B (d) 7.28 J(8.52)
C (q) 5.28 J(6.64)
D (d) 1.89 J(6.64)
Br
O
7.94
7.91
7.30
7.27
7.26
5.31
5.29
5.27
5.25
2.42
1.90
1.88

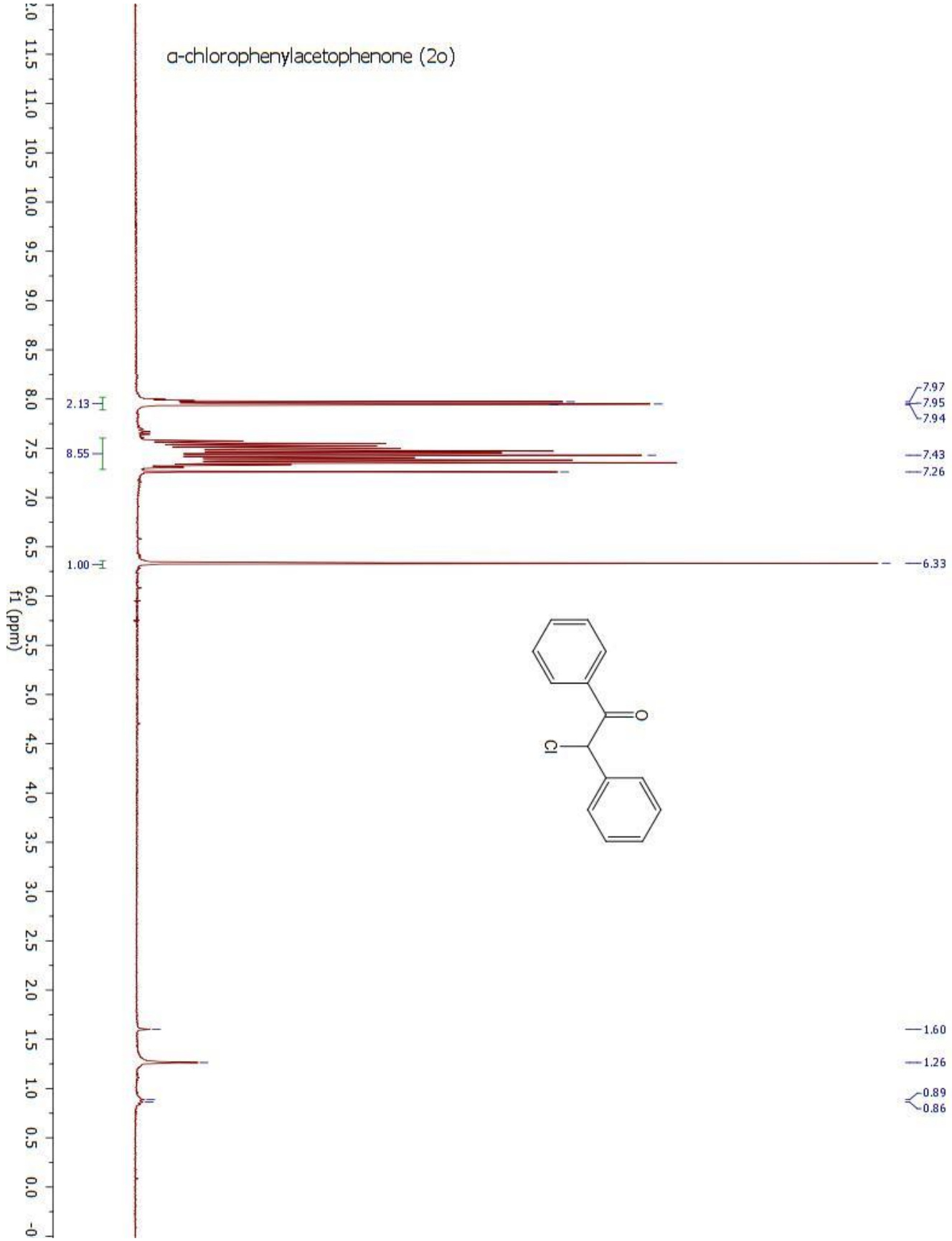

2-bromo-1-(p-tolyl)propiophenone (2l)
193.14
144.81
131.60
129.58
129.17
77.59
77.16
76.74
41.66
21.85
20.30
O
Br
f1 (ppm)

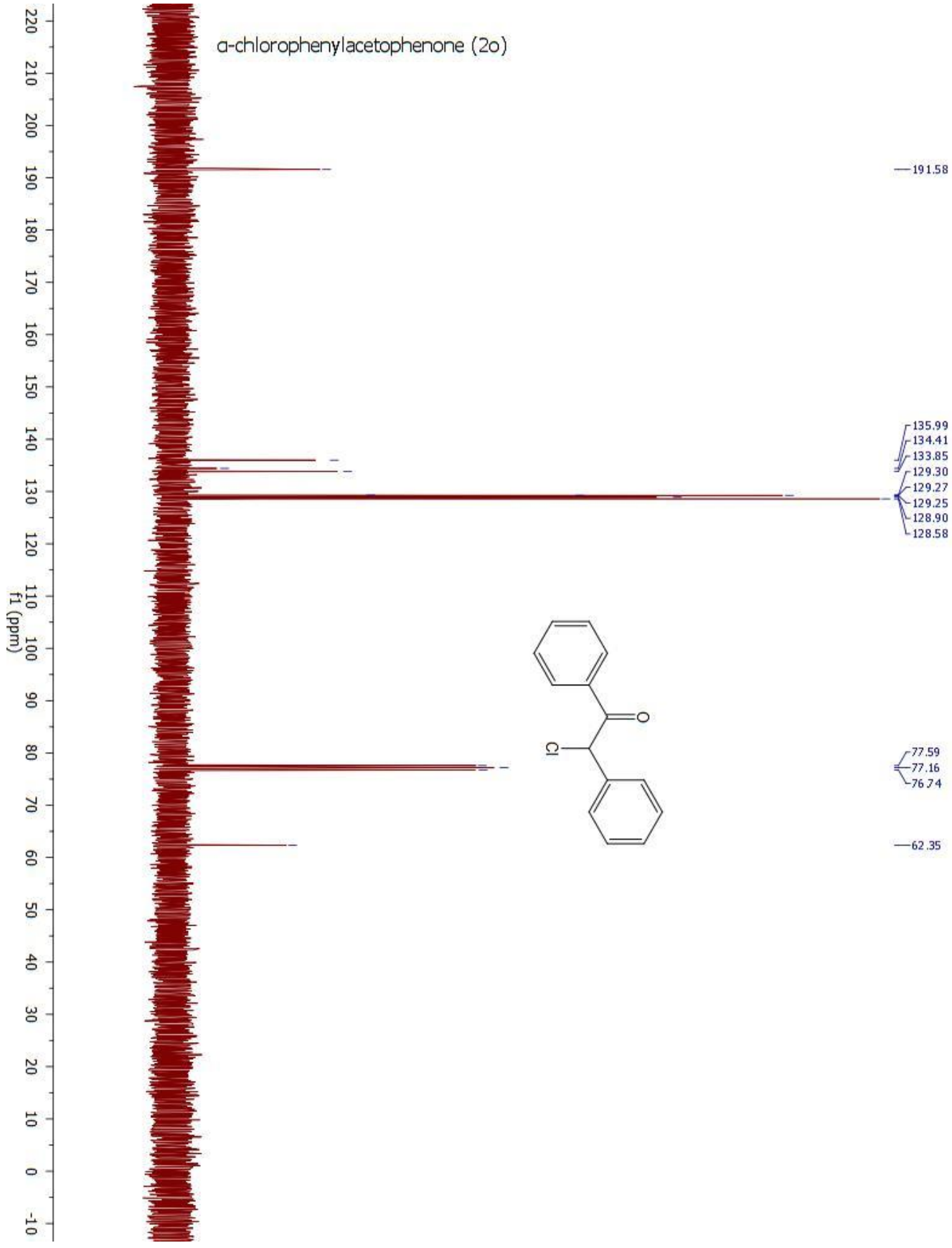

α-chloro-p-methoxypropiophenone (2m)
f1 (ppm)
1.96
1.96
1.00
2.99
2.99
8.02
7.99
7.26
6.98
6.95
5.25
5.23
5.21
5.19
3.89
1.75
1.72
1.56
O
O
Cl

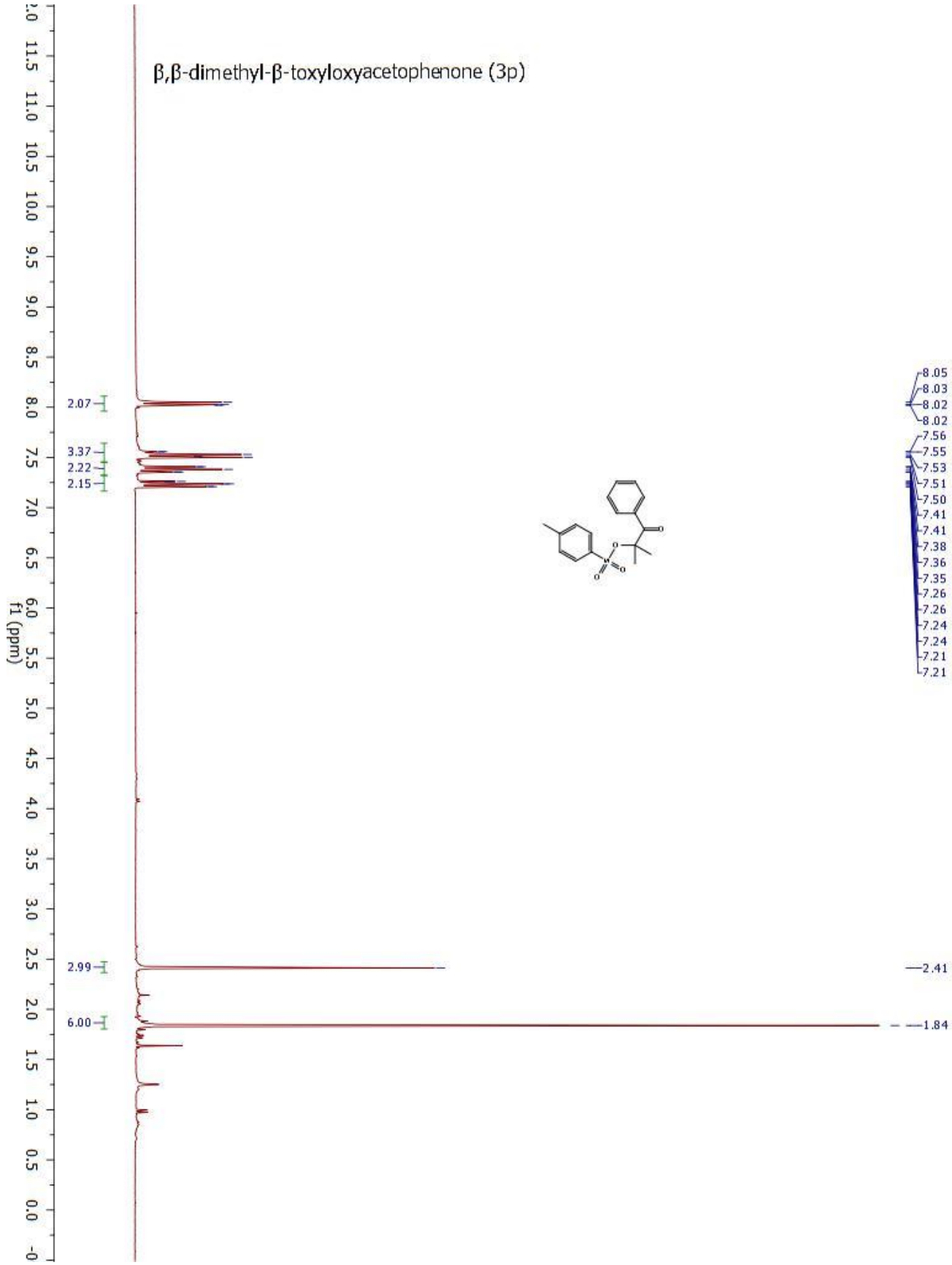

α-chloro-p-methoxypropiophenone (2m)
192.35
164.14
131.54
127.13
114.13
77.58
77.36
77.16
76.74
55.70
52.81
20.24
f1 (ppm)
O
O
Cl

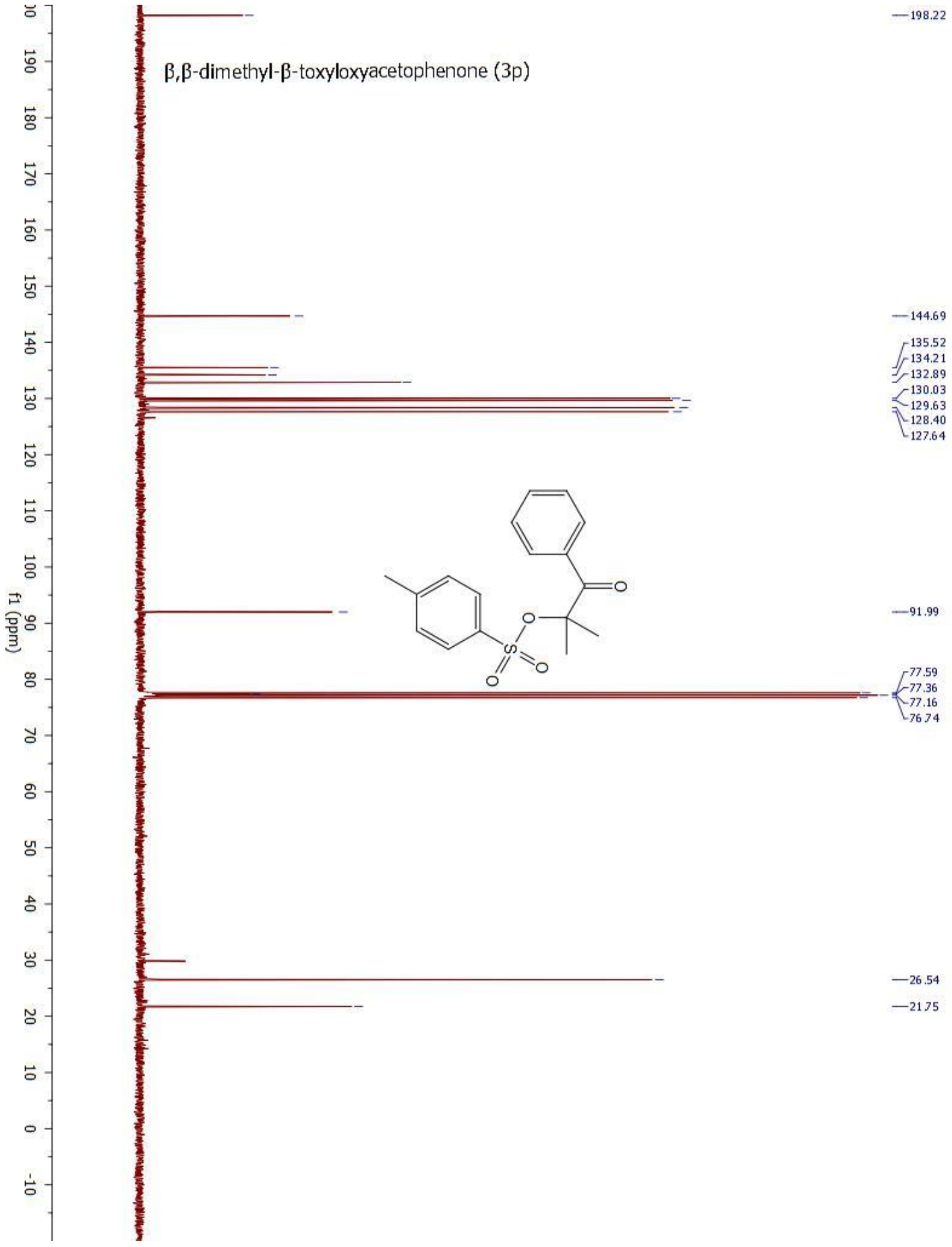

α-chloro-m-(trifluoromethyl)propiophenone (2n)
F
F
F
O
Cl
E (d)
8.21
J(7.86)
D (d)
7.86
J(7.81)
C (t)
7.65
J(7.83)
B (q)
5.22
J(6.63)
A(d)
1.77
J(6.63)
1.00
1.00
1.00
1.04
1.03
3.13
8.28
8.22
8.20
7.87
7.85
7.68
7.65
7.26
5.25
5.23
5.21
5.19
1.79
1.76
1.54
f1 (ppm)


α-chloro-m-(trifluoromethyl)propiophenone (2n)
192.41
134.85
132.27
132.25
131.80
131.37
130.93
130.25
130.20
130.16
130.11
129.56
129.10
126.06
126.01
125.96
125.91
125.50
121.89
118.28
77.58
77.16
77.16
76.74
52.71
19.72
B (q)
130.18
J(3.56)
A (q)
125.99
J(3.82)
f1 (ppm)


α-chlorophenylacetophenone (2o)
2.13
8.55
1.00
7.97
7.95
7.94
7.43
7.26
6.33
1.60
1.26
0.89
0.86
O
Cl
f1 (ppm)


α-chlorophenylacetophenone (2o)
191.58
135.99
134.41
133.85
129.30
129.27
129.25
128.90
128.58
77.59
77.16
76.74
62.35
O
Cl
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


β,β-dimethyl-β-toxyloxyacetophenone (3p)
f1 (ppm)
2.07
3.37
2.22
2.15
2.99
6.00
8.05
8.03
8.02
8.02
7.56
7.55
7.53
7.51
7.50
7.41
7.41
7.38
7.36
7.35
7.26
7.26
7.24
7.24
7.21
7.21
2.41
1.84


β,β-dimethyl-β-toxyloxyacetophenone (3p)
198.22
144.69
135.52
134.21
132.89
130.03
129.63
128.40
127.64
91.99
77.59
77.36
77.16
76.74
26.54
21.75
f1 (ppm)